

RSRB GUIDANCE FOR INVESTIGATORS

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Scope and Purpose of the RSRB

The University's Research Subjects Review Board (RSRB) reviews all human subject research conducted by University of Rochester faculty and staff – regardless of where the research occurs.

⇒ **Key terms:**

- **Human subjects**
- **Research**
- **Intervention**
- **Interaction**
- **Private Information**
- **Test article**

The federal regulations provide these definitions:

- Human subject research is any activity that either:
 - Meets the DHHS definition of research and involves human subjects as defined in the DHHS regulations; OR
 - Meets the FDA definition of research and involves human subjects as defined in FDA regulations.
- Research as defined by DHHS regulations: A **systematic investigation**, including research development, testing and evaluation, designed to develop or contribute to **generalizable knowledge**. A “systematic investigation” generally means that there is a study plan/protocol that is followed. Contributing to “generalizable knowledge” means that there is or will be a report, publication, poster, communication, etc. that provides the results and conclusions of the research to other people/clinicians/researchers.
- Research as defined by FDA regulations: Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the Food, Drug and Cosmetics Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. For research involving drugs, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.
- Human subject as defined by DHHS regulations: A **living individual** about whom an investigator (whether a professional or student) conducting research obtains:
 - Data through intervention or interaction with the individual, or
 - Identifiable private information
- Human subject as defined by FDA regulations: An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices, a human subject is also an individual on whose specimen an investigational device is used.
- Intervention: Includes both **physical procedures** by which data are gathered (for example, venipuncture) and **manipulations of the subject or the subject's environment** that are performed for research purposes.

- ***Interaction:*** Includes **communication or interpersonal contact** between the investigator and the subject.
- ***Private information:*** Information about behavior that occurs in a **context in which an individual can reasonably expect that no observation or recording is taking place**, and information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical, employment and educational records).
- ***Test article:*** Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Food, Drug and Cosmetics Act or under sections 351 or 354-360F of the Public Health Service Act.

NOTE: These definitions also apply to research on human specimens and review of records containing human subject information.

The Federalwide Assurance

The RSRB is charged with reviewing human subject research under its Federalwide Assurance, or FWA -- an agreement between the University and the U.S. Department of Health and Human Services (DHHS) Office of Human Research Protection (OHRP).

A few notes about the assurance:

- What is it?
 - The assurance is the University's written confirmation to the federal government that it will comply with regulations and principles pertaining to the ethical treatment of human research subjects.
- Why is it so important?
 - The ethical principles in the assurance provide the basic framework within which the University seeks to protect human research subjects.
 - Without the assurance, the University is not permitted to conduct federally funded research.
 - If the terms of the assurance aren't honored, all federally funded research at the University can be shut down by the government.
- Who does it apply to?
 - Institutional officials, investigators and the RSRB
- Does it apply to all research?
 - Under the terms of our assurance, the University has agreed to apply to all research the basic federal protections of 45 CFR 46, Subpart A, which includes the requirements for RSRB review and informed consent.
- How long is it in effect?
 - The assurance (FWA00009386) is renewed for three-year terms. The most recent expiration date can be found on the RSRB web site.

The University has established a system of ethical review boards (RSRB) to review research projects involving human subjects. Each board consists of representatives from a variety of scientific and non-scientific disciplines, and community members. The primary function of the RSRB is to protect the rights and welfare of human subjects and to assist investigators in this process. Investigators bear the primary responsibility for ensuring that research protocols meet the standards established by federal and state regulations, and University policies (including requirements of RSRB approval).

Before any research project involving human subjects can start, it must first be reviewed and approved by the RSRB, and then conducted according to the guidelines set forth in this document. This compliance is a crucial element of the RSRB approval process because it is the collective effort of individual investigators in this area that ensures the integrity of the University as a research institution.

The University has four internal boards to review research conducted by its investigators, as follows:

- Behavioral and Social Sciences board (meets monthly)
- AIDS and Oncology (meets weekly)
- Two biomedical boards (meet bi-weekly)

Western IRB (WIRB) serves as the university's IRB of record for industry-sponsored, industry-initiated research of FDA-regulated drugs and devices posing greater than minimal risk.

a) **Ethical Principles Guiding the RSRB**

In 1974, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission published the ***Belmont Report***, which sets forth the basic ethical principles that guide the conduct of research with human subjects. Three principles were defined in the report as basic to the protection of human subjects:

⇒ **Key terms: respect for persons, beneficence, justice**

The University is guided by these principles:

- **Respect for Persons** To demonstrate respect for persons, investigators are required to seek voluntary informed consent from potential subjects before conducting any research procedures, and to ensure that subjects remain informed as the study progresses. Voluntary informed consent means that subjects are afforded a free choice to decide about participation, and the study is fully described in terms that are easy for them to understand. The consent form should include enough information about the study risks and benefits to help prospective subjects decide whether to take part in the research.

Respect also means honoring the privacy of individuals and maintaining the confidentiality of data obtained. Respect for persons with incapacities, children and mentally disabled persons, for example, requires taking extra precautions to protect these individuals – even if it means excluding them from participation in certain research. The degree of protection depends on the level of autonomy each prospective subject possesses, as well as the degree of risk posed by the research.

- **Beneficence:** The principle of beneficence requires that researchers maximize the potential benefits to the subjects and minimize the risks of harm. Designing sound research and conducting it according to the approved study plan are ways to maximize potential benefits to both society and individual subjects. Direct benefits to the subjects --

or generalized knowledge gained from the research -- should equate with or outweigh the risks presented by the research. For example, some drug studies pose significant risk to subjects from side effects, but those risks are balanced with the potential for disease remission. In all cases, steps must be taken to minimize the risks that exist. The risk/benefit analysis applies to all studies, whether they involve minimal or greater-than-minimal risk.

- **Justice:** Subjects must be selected fairly, with the risks and benefits of research distributed equitably. Investigators should take precautions not to select subjects simply because of their easy availability, their compromised position, or because of social, racial, gender, economic or cultural status that is not related to the research question. Investigators should establish scientifically valid inclusion criteria based on those factors that most effectively and soundly address the research problem.

The principle of justice likewise dictates that certain subject populations – for example, pregnant women or those whose first language isn't English – are not automatically excluded from research projects through the design of procedures that do not place barriers to participation. Both inclusion and exclusion of subjects to research studies need to be justified on sound scientific principles, not financial or practical concerns.

The Belmont Report makes a distinction between research and treatment – it is on this distinction that the RSRB bases its guidance on consent form wording e.g. –

- “Research subject” -- *not* “patient”
- “Investigator” – *not* “doctor”

Click here to read the Belmont Report:

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

b) Federal Regulations and their Application

In addition to reliance on the ethical principles of the Belmont report, the RSRBs review research in accordance with:

- Food and Drug Administration (FDA) regulations published at 21 CFR 50 and 56,
- Health and Human Services (HHS) regulations published at 45 CFR 46, and the “Common Rule” regulations published at 45 CFR 46, Subpart A
- FDA regulations at 21 CFR 312, 600, 812 and 814, regarding investigational new drugs and investigational devices, as applicable
- 45 CFR 160 and 164, the “Privacy Rule” regarding the Health Information Portability and Accountability Act (HIPAA)
- 42 USC § 289 (vs. 498A(b)(1)) (regarding fetal tissue research)
- Article 24-A of the New York State Public Health Law (Protection of Human Subjects)
- § 79-L of the New York State Civil Rights Law (pertaining to genetic research)

In the review of research projects, the RSRB must be assured that:

- 1) Risks to subjects are minimized, a) by the use of procedures consistent with sound research design which do not expose subjects to unnecessary risk, and b) when appropriate, by the use of procedures already being performed on the subjects for diagnostic or treatment purposes.

Note: To ensure that risks to subjects are minimized and benefits are maximized, the RSRB seeks to confirm that studies employ sound research design.

- 2) Risks to subjects are reasonable in relation to any benefits that might be expected from participating and to the importance of the knowledge that may result.
- 3) Selection of subjects is fair and equitable. The RSRB seeks to determine that no eligible individuals are denied the opportunity to take part in any study, particularly those from which they may benefit, based on arbitrary criteria such as sex, age, or social or economic status. Similarly, no one group should be disproportionately burdened by assuming the risks of a study that would be more widely generalizable. The RSRB looks for adequate safeguards for vulnerable subjects (protection against undue influence).
- 4) Participation is voluntary and informed consent is obtained from each prospective subject, or, where appropriate, from the subject's authorized representative and that consent is appropriately documented.
- 5) When appropriate, the research plan provides for monitoring the data collected to protect the safety of subjects.
- 6) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Pre-Review Considerations

Before submitting a study to the RSRB for approval, consider the following questions:

Who can be a Principal Investigator?

According to the University of Rochester **Principal Investigator Eligibility Policy**, a Principal Investigator (PI) is the individual who has full and final responsibility for the conduct of the project as proposed. The PI must comply with the terms, conditions and policies of both the sponsor and the University, including the submission of all required reports. **All correspondence from the RSRB pertaining to the research is directed to the Principal Investigator.**

PIs must hold full-time faculty positions or full-time positions enjoying similar rights and privileges (e.g., Senior Scientist, Scientist, Senior Research Associate, Senior Technical Associate, Research Associate, Instructor, etc.) Part-time clinical faculty in the School of Medicine and Dentistry and the School of Nursing having the rank of Assistant Professor or above may also be named as Principal Investigators, if the research is conducted as part of their University activities.

NOTE: Principal Investigators on studies that the RSRB determines are exempt need not hold a faculty position (e.g., students may serve as PIs on exempt studies).

Anyone who does not meet the criteria described above may not serve as a Principal Investigator. This includes adjunct professors, residents, fellows, students or staff members, *even if* they are identified as the Principal Investigator by the funding source or regulatory body (e.g., NIH/NSF grant or FDA-approved Investigational New Drug applications or Investigational Device Exemptions). Such individuals may serve as co-Principal Investigators under the aegis of a UR-recognized and approved PI who assumes ultimate responsibility for the research.

Rarely, exceptions to the Principal Investigator Eligibility Policy may be made with the approval of both the investigator's Department Chair and Dean under the following considerations:

1. A petition to serve as a Principal Investigator must be for a specific project and not as a routine procedure. The approval must be for a specific project and duration, and will be valid for multiple funding applications.
2. The individual must have the necessary experience and expertise.
3. The individual must obtain written commitments to guarantee necessary laboratory space or other resources or support.
4. A plan should be developed for administering a sponsored program and should, at a minimum, identify a specific individual who will assume the responsibilities of the Principal Investigator, and whether or not the project will stay at the University.

Please refer to the Office of Research and Project Administration Principal Investigator Eligibility Policy (<http://www.rochester.edu/ORPA/policies/pieligib.pdf>)

Does the project involve human subjects? Does the project involve research?

It's often easy to determine whether a project involves research -- a randomized trial, for example, or testing a drug for the first time in humans. But there are also times when it may be more difficult to tell whether an activity qualifies as research.

Before submitting your application to the RSRB, consider these brief definitions of research:

- Per HHS: A systematic investigation (including research development, testing and evaluation) designed to contribute to generalizable knowledge.
- Per FDA: An experiment involving a test article (drug, biologic, device, food or color additive, electronic product) and people who either receive the test article or serve as controls.

These definitions note that two key elements are present in research:

1. Some form of study design is necessary. This is usually written in a protocol or study plan. A report of an interesting case or occurrence is not *research*, because there was no study plan; however, a retrospective review of records looking for patterns meets the criterion for research because it would have a study plan. For FDA-regulated research, the study plan (protocol) may be written by the sponsor, a cooperative study group or the investigator – regardless, the UR investigator is responsible for following the protocol as approved by the RSRB.
2. Research is designed to contribute new knowledge to science and society (i.e., *generalizable knowledge*). The *new knowledge* may be proving a hypothesis, showing that a drug or device works, reporting on results of certain activities (controlled or naturally occurring), and so forth. The knowledge that results from research often drives other research projects, further contributing to science and benefiting society. Activities such as quality assurance and service provision, intended only to benefit a defined group (e.g., a hospital system, a business, a student class) or an individual (e.g., patient care, student instruction), even if innovative or unconventional, are not designed to contribute to generalizable knowledge, and thus don't meet the definition of research.

Consider your *intent* – in an overall sense – not just, “Do I intend to publish?” but “Would I conduct this project as planned if I knew I would never receive any form of academic recognition for it?”

“If the lack of academic recognition would affect the conduct of the project, then research intent is a primary motive for the activity.” (Amdur & Bankert, 2006)

Think about what *isn't* research (Amdur & Bankert, 2006):

- **Medical practice:** designed to enhance the well-being of a patient or others. Includes **innovative therapy** – still designed to benefit an individual patient, but “the desired outcome is to some degree unproven.” **Medical practice for the benefit of others** – donating blood, for example, in which the goal “is to benefit a well-defined group of people in a predictable way.”
- **Public health practice:** e.g., surveillance (monitoring of diseases) and program evaluation (immunization coverage, or clinical preventive services such as mammography).
- **Quality assessment** – activities that determine whether aspects of medical practice conform to established standards.
- **Outcome analysis:** “projects in which medical records are reviewed to evaluate the outcome of medical treatment or the course of patients with a specific medical condition.” Results are not compared to an established standard.

- **Resource utilization review:** “Medical record review...conducted to evaluate the use of resources in a specific health care activity.”
- **Education:** transferring information from one group of people to another – i.e., teaching.
- **Case report or case series:** A retrospective report on a medical treatment (including innovative treatment). A medical case study is a report of treatment (including innovative treatment, e.g., surgery), and, as such, does not meet the Common Rule definition of research (a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge).

If any of the following is present, the activity is considered research rather than a case study:

- There is a plan to perform the treatment on some individuals but not on others.
- Investigational drug(s) or device(s) are involved (off-label use of an approved drug or device is permissible).
- There is a clear intent before treating the patient to use systematically collected data that wouldn't ordinarily be collected in the course of clinical practice in reporting and publishing the case study.
- There is intent to manipulate medications (even approved ones) to determine maximum effectiveness, or to test if they work consistently well.
- Extra tests are conducted for the sake of reportability.
- There is a protocol/study plan.
- Separate sets of records or data sheets are maintained (particularly with identifiers).
- The primary purpose is to answer a research question, not to provide care.
- There is consideration that the treatment might yield a case series if it is effective in others (e.g., testing a hypothesis).

Case studies may be published; but must be descriptive, not analytical.

Remember that the RSRB oversees only research involving living human beings.

If, after reviewing this information, you still have questions, contact the RSRB Office (585-275-2398), which will apply the federal regulations to determine whether your project involves research. We can sometimes answer questions over the phone, but we may need written materials and/or to discuss the proposal at a face-to-face meeting.

Amdur, R. J., Speers, M., & Bankert, E. (2006). Identifying intent: Is this project research? In R. J. Amdur & E. A. Bankert (Eds.), Institutional review board management and function (pp. 101-105). Sudbury, MA: Jones and Bartlett Publishers.

Here are some examples of activities that the RSRB may determine are exempt from review (complete an application to ensure proper review):

- Research involving deceased individuals (e.g., autopsy materials or cadavers) or records of deceased individuals. (Note: HIPAA and New York State regulations may still apply to research involving deceased individuals.)
- Non-research activities, such as quality improvement projects. Projects undertaken for the purpose of quality improvement generally do not need to be submitted to the RSRB for review, unless external presentation or publication of the results is anticipated.

- Training grants that support individuals, or institutional grants that support general programs. (**Note:** If human subject research is conducted under this type of grant, each individual project must be reviewed and approved before it begins.)
- Classroom exercises that are used by faculty to teach techniques and that do not generate new knowledge. However, presentation of these activities outside of the classroom, or publication of the student-prepared documents, is considered research.

Investigator Training

All investigators (including students) and persons obtaining consent or other key study personnel who have contact with subjects must complete training in research ethics. The University's Office of Human Subject Protections (OHSP) administers the program providing research ethics training. There are two programs:

- 1) **Human Subject Protection Program (HSPP)** - for investigators and research staff conducting research that involves greater than minimal risk
- 2) **Ethical Principles in Research Program (EPRP)** - for investigators and research staff conducting minimal or less-than-minimal risk research

NOTE: Completion of the HSPP certification also meets the EPRP requirement.

For details on research ethics training, go to the Office of Human Subject Protection website at <http://www.urmc.rochester.edu/ohsp/>

Who Reviews What?

⇒ **Industry-sponsored, industry-initiated research**

Western Institutional Review Board (WIRB) is the University's IRB of record for nearly all research involving *industry-sponsored, industry-initiated, FDA-regulated drugs and devices posing greater than minimal risk*. These studies, referred to as "clinical trials," are generally conducted as part of obtaining FDA approval for marketing drugs and devices.

The RSRB has prepared a letter to address sponsor requests regarding WIRB's role in reviewing research for the University. View the letter at: http://www.rochester.edu/rsrb/documents/pdf/IRB_of_Record.pdf

⇒ **Investigator-initiated research**

The RSRB reviews all investigator-initiated research, regardless of sponsorship. This includes, for example: foundation- and federally funded studies (whether alone or in combination with industry sponsorship); unfunded or departmentally sponsored research, or industry-sponsored, investigator-initiated studies.

Note: "Investigator-initiated" applies to the individual(s) who wrote the study protocol, *not* to the location. For example, an industry-sponsored protocol written by an investigator at an out-of-state university or medical center would be considered "investigator-initiated," and reviewed by the RSRB.

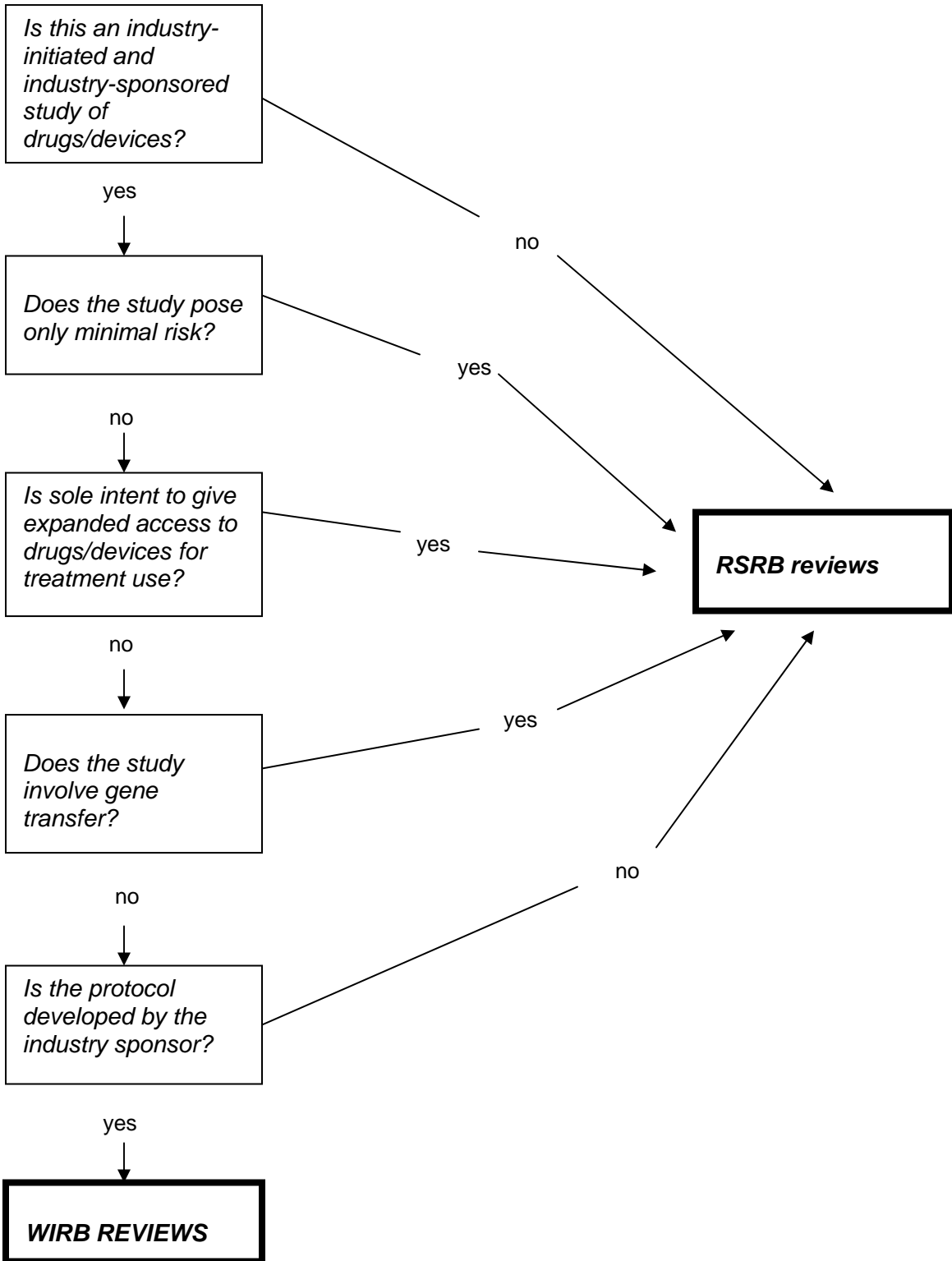
Exceptions:

The following exceptions apply:

- Research involving **gene transfer**, regardless of funding source, is reviewed by the RSRB.
- **Single patient use and expanded access treatment** protocols, regardless of funding source, are reviewed by the RSRB.
- **Minimal risk** protocols that are part of, or a follow-on to studies originally reviewed and approved by WIRB, are reviewed by WIRB.

NOTE: The RSRB charges a fee for the review of industry-sponsored studies.
The fee schedule is on the RSRB web site.
<http://www.rochester.edu/rsrb/apply-rsrb/feeSchedule.html>

Who Reviews What? WIRB or RSRB?



Does the protocol qualify for Just-in-Time Review?

Most federally funded (and some foundation-funded) research qualifies for Just-in-Time review. This means that RSRB review and approval are deferred until the investigator is notified that the study is within the fundable range. If your project qualifies for Just-in-Time review and you have not yet received written documentation (or email) that it is within the fundable range, wait to submit the application to the RSRB until you've received that notification. As soon as you receive notice of possible funding, submit the [RSRB online application](#) to ensure ample time to complete the review process.

Click here for the Just-in-Time review policy:
<http://www.rochester.edu/rsrb/documents/pdf/JIT.pdf>

Is any member of the study team part of the University's covered entity?

The federal Health Information Portability and Accountability Act (HIPAA) has established regulations (the Privacy Rule and the Security Rule) regarding the use of Protected Health Information (PHI) in research. If research is subject to these Rules, compliance with those requirements is necessary.

Refer to the "HIPAA Guidelines" in the menu on the right hand side of the RSRB website:
<http://www.rochester.edu/rsrb/>

Does the Study need Data Monitoring?

Data and Safety Monitoring Plans

A Data and Safety Monitoring Plan is a system of appropriate oversight and monitoring of the conduct and progress of the study to ensure:

- 1) that important information that may affect the safety or welfare of subjects comes to light and is acted upon as quickly as possible, and
- 2) the validity and integrity of the data.

The RSRB will require data and safety monitoring consistent with 45 CFR 46.111(a)(6) and 21 CFR 56.111(a)(6) which state, "where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. NIH Guidelines specify that all clinical trials should have a system in place for oversight and monitoring to ensure the safety of subjects and validity of the data.

Monitoring activities should be appropriate to the nature, size and complexity of the trial. The investigator is responsible for ensuring that there is an appropriate data and safety monitoring plan (DSMP) in place, documenting the function of the plan in the protocol, and ensuring that this plan is followed.

NOTE: The RSRB requires a data and safety monitoring plan for all research studies involving greater than minimal risk. The plan must be described in the protocol.

While the safety of each study must be ensured, not every study requires a formal data and safety monitoring board (DSMB), but rather an appropriate *plan* (DSMP). The level of risk will determine who is responsible for safety monitoring, as described below.

The Data and Safety Monitoring Plan can take the following forms:

- **Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC):** a formal committee, independent of the trial organizers and investigator(s), that is specifically established to conduct: 1) interim monitoring; 2) oversight and analysis of study information and data to assure the continuing safety of research subjects; 3) efficacy of the study intervention; 4) appropriateness of the study; 5) continued relevance of the study question, and 6) integrity of the accumulating data throughout the life of a research project.
- **Monitoring by the Principal Investigator only:** This level of monitoring would be appropriate for minimal risk or other studies that can be effectively monitored by the PI. The prompt reporting of unanticipated problems and other stud-related safety information is made to the RSRB, sponsor, or other agencies, as needed. Protocol deviations and amendments are reported. Examples of study activities appropriate to this level of review:
 - Blood draws
 - Observational studies
 - Studies involving non-invasive collection of data, e.g., CT/MRI/DEXA scans/ECG
 - Surveys/questionnaires
 - Open-label, single-site clinical trials
 - Small pilot studies with drugs/devices
 - Phase IV drug or device studies
- **PI monitoring and independent safety monitor:** The PI monitors the study as noted above, with additional oversight by a safety monitor. This individual has appropriate clinical and research expertise and should have no conflicts in monitoring the study. This level of monitoring would be appropriate for studies posing greater than minimal risk that may require independent safety monitoring. Examples of study activities appropriate to this level of review:
 - Phase I or II studies
 - Investigator-initiated study involving potential undue influence in a vulnerable population
- **PI monitoring and formal DSMB:** The PI monitors the study as noted above, with oversight by a Data and Safety Monitoring Board. The protocol should contain a description of the DSMB, its composition (names of the chair and its members, if known), frequency of meeting, and specific responsibilities. Examples of study activities appropriate to this level of review:
 - Multicenter clinical trials
 - Gene transfer studies
 - Testing of a new drug or device for which there is little or no safety data in humans
 - Blinded placebo controlled clinical trials

A data and safety monitoring plan may also be appropriate for behavioral studies. *Remember that risks are not limited to biomedical studies.* Consider these risks posed by behavioral research:

- **Breach of confidentiality:** This is often the greatest risk to subjects. If confidentiality is not maintained and information from the study becomes known by individuals outside the research, subjects may face harm to their reputation, jeopardy to employment or insurance, or legal harms.

- **Risks of study procedures:** Consider psychological stress such as painful memories, anxiety, fear, confusion, depression, or suicidal ideation.
- **Location of the research:** Subjects in other countries may face risks by answering questions that are politically or socially sensitive, for example.

NOTES:

- All **NIH-funded Multicenter Phase III clinical trials** must have a DSMB. Consult the web pages of each Institute for guidance.
- All **protocols conducted at the Clinical Research Center (CRC)** must have an approved data and safety monitoring plan. Refer to the CRC website for further information: <http://urmc.rochester.edu/ctsi/research/crc/forms.cfm>

When a DSMB Is Needed

All clinical trials require safety monitoring, but not all trials require a DSMB. FDA guidance (<http://www.fda.gov/ohrms/dockets/98fr/010489gd.pdf>) specifically states that DSMBs should be established for controlled trials where mortality and major morbidity serve as the primary or secondary endpoints. Other major factors to consider regarding the establishment of a DSMB are outlined below. Research subject safety is of the utmost importance.

If any of the following questions are answered yes, FDA guidance suggests a DSMB may be warranted:

Subject Safety

- Is mortality or major morbidity an endpoint?
- Would positive or negative results during the study require termination for ethical reasons?
- Is there little knowledge regarding the safety of the intervention (drug/device), or is there knowledge of safety concerns (potential toxicity)?
- Is the targeted study population fragile, e.g., seriously ill, elderly, children, pregnant women, where there may be an increased risk?
- Is the study a large, multi-center trial, with a long duration, where subjects would have greater exposure possibly resulting in adverse events that would not be as easily identified in single-center studies with shorter durations?

Practicality

- Is the study a short-term trial where a DSMB would not have adequate time to conduct assessments?
- If the study is a short-term trial where subject safety is a concern, are there mechanisms in place where a DSMB would be notified quickly of unexpected events/results? (Note: FDA guidance recognizes that many clinical trials evaluate interventions to relieve symptoms. These studies are usually of short duration and smaller than major outcome studies. DSMBs usually are not required to monitor these types of trials.)

Scientific Validity

- Would changes in the understanding of the disease process, the target population or new treatment discoveries warrant changes to the trial as it progresses?

Composition of DSMBs

There is a tremendous amount of responsibility placed on the DSMB in terms of its power to make recommendations based upon the data it receives from the trial itself as well as from external sources. It is usually the trial sponsor or trial steering committee that appoints the DSMB members. In all cases, DSMB members should be free of conflicts of interest or any perceived conflicts (e.g., financial, scientific or intellectual).

These boards are typically made up of individuals who have expertise in ethics, the field of investigation, experience in the proper conduct of clinical trials, statistical knowledge, and who do not have any conflicts of interest (i.e., financial, intellectual or professional) with the research they oversee. As a group, the DSMB acts as an independent review/advisory board whose primary mission is to measure and report on the continuing safety of research subjects. The DSMB accomplishes this by meeting regularly and reviewing the accumulating data in an ongoing clinical trial. Through this process, the DSMB also assesses the continuing validity and scientific merit of the trial.

FDA guidance suggests that the following factors be used to consider the selection of DSMB members:

- Relevant expertise (clinical specialty, biostatistician, pharmacologist, toxicologist, bioethicist)
- Previous DSMB experience
- Clinical trial experience

Administration of DSMBs

Each DSMB should establish operating procedures before the study starts. Consider the following factors:

- Meeting schedule/frequency (based on expected rates of accrual/risks to subjects)
- Reporting frequency and types of reports to be generated
- Meeting structure - open session to allow investigator and sponsor attendance versus closed session where blinded and confidential information is discussed
- Format of the interim reports
- Statistical methods to be used for the interim analyses

DSMB Responsibilities

The main responsibility of a DSMB is to review accumulating data from an ongoing clinical trial on a regular basis. After thorough analysis of the accumulated data, the DSMB may advise the sponsor and/or investigator regarding the continuing safety of subjects in the trial and of those yet to be recruited, as well as the continuing validity and scientific safety of the trial.

NOTE: The DSMB is responsible for recommending trial termination when subject safety is jeopardized.

The DSMB accomplishes this by:

Safety Monitoring

- Interim review of adverse events in each arm of the study
- Making judgments on early termination of a trial when based on the types and extent of adverse events if the risks outweigh the benefits

Monitoring for Effectiveness

- It is important in studies with serious outcomes that any treatment advance is made available as soon as possible but only when based on the predetermined statistical monitoring plan.
- It is just as important to terminate a study when the predetermined endpoint has no chance of being achieved.

Monitoring Study Conduct

- Reviewing and assuring that rates of recruitment are adequate
- Assessing whether eligibility requirements are being met
- Ensuring protocol adherence and reviewing protocol violations
- Verifying completeness and timeliness of the data reported/accumulated
- Evaluating retention/dropout rates (as they affect interpretation of study results)

Monitoring External Data

- Reviewing results of related studies, which may affect the design of the ongoing study or its continuation/alteration

Making Recommendations

- The primary responsibility of a DSMB is to make recommendations to the sponsor and/or investigator regarding the continuation of the study. These recommendations could include continuation, modification, temporary suspension of enrollment or intervention or terminating the study
- Recommendations, supported by a rationale, should be documented in a clear, concise manner for review by the sponsor, investigator and or regulatory agency

Maintenance of Records

- Keep minutes of all meetings and report minutes during the study and for the required length of time after closure.
- DSMB meeting minutes typically contain two parts, depending on confidentiality of the information (unblinded comparative data) being discussed, i.e., the open and closed parts of the meetings are kept separate.

Regulatory Safety Reporting Requirements

Studies conducted under an Investigational New Drug application (IND) or Investigational Device Exemption (IDE) are subject to safety reporting requirements. These requirements include the reporting of serious unexpected events to the FDA by the sponsor. There may be instances

where a DSMB may detect a greater frequency of serious adverse events in one arm of a controlled study. This finding, reported to the sponsor as part of a recommendation to modify the study, would be considered serious and unexpected, and the sponsor would be required to report this to the FDA as well as to all other study investigators.

a) Investigator Responsibilities

In studies where DSMBs are involved, the investigator is still responsible for identifying potential adverse events experienced by the local study subjects and reporting them to the sponsor.

When the investigator is the sponsor of the clinical research study (i.e., holds the IND or IDE), the investigator assumes all the roles of a sponsor in addition to that of the investigator. Refer to "Sponsor and Sponsor/Investigator Responsibilities" below.

b) RSRB Responsibilities

After its initial approval of studies, the RSRB is responsible for reviewing information both from the study site and external sources to ensure the continued acceptability of the trial. The RSRB may confirm that the investigator is following the data monitoring procedures described in the protocol. The RSRB may take actions based on the recommendations of the DSMB.

A DSMB report indicating an increased risk to subjects (usually reflected as a revision to the protocol or consent) are to be submitted to the RSRB within 15 calendar days of the investigator receiving it. Such reports are to be filed with the request for amendment. All other DSMB reports (e.g. those allowing the study to continue unchanged) are to be submitted with the progress report at the time of continuing review.

c) Sponsor and Sponsor/Investigator Responsibilities

The trial sponsor is responsible for thoroughly reviewing the recommendations of the DSMB and taking appropriate actions regarding modifications or termination of the study. In addition to determining when a DSMB is needed and the appointment of individuals to serve on the DSMB, the following are usually the procedures undertaken by the sponsor:

- Appointing the committee chair
- Establishing procedures to assess potential conflicts of interests of potential members
- Ensuring the confidentiality of the interim data analyses
- Establishing or approving DSMB Standard Operating Procedures (SOPs), i.e., meeting schedules, format of reports, statistical methods
- Submission to FDA of all DSMB meeting records and interim reports
- Notifying FDA and the investigators of any recommendations or requests made by the DSMB regarding the safety of the participants
- Consulting with FDA before accessing interim data, terminating the study or modifying the protocol (could affect the validity of the study)

Additional Approvals

⇒ *University Committees*

In addition to RSRB review, these university committees require review and approval of certain research projects:

- 1) **Cancer Center Clinical Trials Office (CTO):** approves hematology/oncology related studies proposed at the University of Rochester and its affiliates. CTO approval is also required if the PI or co-PI are hematology/oncology faculty, or if the study involves subjects with cancer. Contact the Clinical Trials Office at (585) 275-5345 for further information.
- 2) **Clinical Research Center (CRC):** if any part of the study is conducted at or uses any resources of the CRC. Note: RSRB review will not begin until after CRC issues approval. The CRC application is contained within RSRB online Submission System. If you have any questions regarding the CRC sections of the application, contact the CRC directly at (585) 275-6409.
- 3) **Perinatal Research Committee:** For studies involving pregnant women, women attempting to become pregnant, or infants in the normal nursery or neonatal intensive care unit at Strong Memorial Hospital or Highland Hospital. Contact (585) 275-7480 for further information.
- 4) **Emergency Department Research Committee:** For studies involving subjects in the Emergency Department or Emergency Medicine Faculty. Contact (585) 463-2970 for further information.
- 5) **Institutional Biosafety Committee (IBC):** For studies involving: 1) introduction of recombinant DNA (plasmids) or gene transfer vectors (including viral vectors) into human subjects; 2) introduction of genetically engineered micro-organisms or infectious agents into human subjects, including live vaccines if they are experimental in nature or not FDA-approved for use in the specific human study population; or 3) analysis of, or experimentation with, sera, blood products, or other specimens derived from humans in any UR lab that is not accredited within the College of American Pathologists [CAP] or the Joint Commission on Accreditation of Healthcare Organizations [JCAHO]. Contact the Institutional Biosafety Committee at (585) 275-3014 or (585) 275-2402 for further information.
- 6) **Surgical Pathology:** For use of slides or tissue from the Pathology Department. Note: Surgical Pathology will review the study after RSRB approval.
- 7) **HURC/RDRC:** For human use of radioactive materials or ionizing radiation-generating devices for research purposes. Contact (585) 275-1473 for further information.
- 8) **Rochester Center for Brain Imaging (RCBI):** For any studies conducted at RCBI. <http://www.rcbi.rochester.edu/research/>
- 9) Highland Hospital **Administrative Research Review Committee (ARRC):** For all studies conducted at Highland Hospital, the ARRC must review and approve the study before enrolling subjects.

NOTE: The RSRB is the IRB of record for research conducted by Highland Hospital investigators. Investigators need to notify the RSRB if their studies will be conducted at Highland Hospital so issues regarding compensation for injury and contact persons can be addressed in the consent form.

NOTE: Ancillary committee approval is a requirement of final RSRB approval. The RSRB's online system automatically blocks the approval of those studies lacking documentation of review and approval by a required ancillary committee.

⇒ ***Institutional Approval***

In accordance with federal guidelines, research approved by the RSRB may be subject to further review and approval or disapproval by University officials. However, these officials may not approve research if it has been disapproved by the RSRB.

⇒ ***Off-site Approvals***

The approval of research by another institution – or another institution's IRB – may be required in addition to approval by the RSRB. The following guidelines apply:

- **Federally funded** research may be conducted only at sites with active, approved Federalwide assurances. This means a site must provide documentation of review and approval – either from its own IRB or the IRB on which it relies.
- **Non-federally funded** research may be conducted at sites that provide documentation of approval:
 - If the site does not have an IRB, the RSRB will request written documentation of administrative approval of the research from the site's signatory official.
 - A site that has an IRB needs to provide written documentation of review and approval of the research.
- **Research conducted in foreign countries**

Because procedures followed by foreign countries to protect human subjects may differ from those used in this country, when research takes place in a foreign country the RSRB will require additional safeguards to demonstrate equivalency. The research must be approved by an appropriately constituted local ethics review committee that uses an acceptable national or international ethical standard as a basis for review. Examples of acceptable standards include:

- the International Conference on Harmonization (ICH) guidelines,
- the World Medical Association Declaration of Helsinki, and
- the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects.

In addition to the documentation of local approval, the informed consent document(s) to be used in the foreign country must be submitted. The RSRB office will review these to ensure that they are comparable to U.S. standards, especially with regard to description

of procedures, risks and explanations of voluntariness. If they are not comparable, changes or appropriate justification will be required. Foreign investigators (co-investigators) must agree to provide timely reports on the progress of the research and to report unanticipated problems to the RSRB (either directly or through the University of Rochester investigator). Federally funded foreign research must also comply with the appropriate agency procedures and regulations (e.g., FWA requirements). Research in foreign countries that differs in human subject considerations from projects conducted in this country or that is not acceptable in this country will not be approved.

Is an Investigational New Drug (IND) or Investigational Device Exemption (IDE) required?

Research Involving Investigational Drugs:

An **investigational drug** is defined as one of the following:

- a. A new drug in any of the clinical stages of evaluation (Phase 1, 2, 3) which has not been approved by the FDA for general use or cleared for sale in interstate commerce
- b. Any marketedly available drug proposed for a new use
- c. Any marketedly available drug to be used in new dosage form or method of administration
- d. Any marketedly available drug that contains a new component
- e. A new combination of two or more marketedly available drugs
- f. A combination of marketedly available drugs in new proportions
- g. Any marketedly available drug involved in a post-marketing surveillance (Phase 4)

Use of Drugs for Off-Label Purposes: Good practice and patient interests require that authorized prescribers be free to use marketedly available drugs according to their best knowledge and judgment. If prescribers use a drug for an indication not in the approved labeling, they have the responsibility to be well informed about the drug and to base its use on a firm scientific rationale and on sound scientific evidence, and to maintain records of the drug's use and effects. Use of a drug in this manner does not require review by the RSRB or FDA notification, despite the fact that the use is technically experimental.

The investigational use of an approved, marketed product differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a study protocol. When the principal intent of the investigational use of a drug is to develop information about its safety or efficacy, RSRB review and approval are required.

Treatment IND: Per 21 CFR 312.34, during the clinical investigation of a drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment IND. The purpose of a treatment IND is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible. FDA permits an investigational drug to be used for a treatment use under a treatment IND if:

- a. The drug is intended to treat a serious or immediately life-threatening disease (defined as the stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment, e.g., advanced cases of AIDS, advanced congestive heart failure, advanced MS);

- b. There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- c. The drug is under investigation in a controlled clinical trial under an IND in effect for the trial (for which the patient is ineligible), or all clinical trials have been completed; **and**
- d. The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence. Use of an investigational drug under a treatment IND must be approved by the RSRB.

Emergency IND: Per 21 CFR 312.36, the FDA can authorize shipment of an investigational drug for a specified use in advance of submission of an IND if there is no time to submit an IND. The specified use must be an “emergency” but not necessarily life-threatening.

NOTE: Documentation of FDA approval or exemption of an investigational new drug (IND) application is required before the RSRB can conduct a review of research requiring an IND.

Research Involving Medical Devices:

Investigational devices are medical devices that are the object of clinical research to determine their safety or effectiveness. Studies undertaken to develop safety and effectiveness data for medical devices involving human subjects must be conducted according to the requirements of the Investigational Device Exemption (IDE) regulations (21 CFR 812).

Investigational devices are classified as either **significant risk** or **nonsignificant risk** devices. In addition to determining whether a study should be approved, the RSRB must determine whether the device presents significant or nonsignificant risk.

Significant Risk Device - one that presents a potential for serious risk to the health, safety, or welfare of the subject. Such a device is intended as an implant; or is to be used in supporting or sustaining human life; or is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health.

- Examples of **significant risk** devices are: catheters (other than urological), ventilators, CPR devices, TMJ prostheses, stents, lithotripters, sutures and absorbable bandages/materials, ECT devices, extended wear contact lenses, pacemakers, contraceptive devices, most laser systems, and most hemodialysis systems.
- Investigations involving significant risk devices must meet the full IDE requirements including the submission of an IDE application to the FDA. As with nonsignificant risk devices, RSRB approval is required prior to conducting clinical trials of an investigational device.

Nonsignificant risk Device - one that does not present a potential for serious risk to the health, safety, or welfare of the subject.

- Examples of **nonsignificant risk** devices are: most daily wear contact lenses, lens solutions, heel cups, antibacterial surgical garments, incontinence devices, oral training splints, and ultrasonic tooth cleaners.
- Unless otherwise notified by FDA, an investigation of a nonsignificant risk device is considered to have an approved IDE if the sponsor fulfills the abbreviated

requirements of the IDE regulations (21 CFR 812.2.b). These regulations require, in part, that IRB approval be obtained and maintained throughout the investigation and that informed consent be obtained and documented.

In deciding if a device presents significant or nonsignificant risks, the RSRB will consider the device's total risks, and not compare these with the risks of alternative devices or procedures. If the device is used in conjunction with a procedure involving risk, the RSRB will consider the risks of the procedure in conjunction with the risks of the device.

Once a decision on the degree of risk is reached, the RSRB will consider whether the study should be approved or not. Some studies involving nonsignificant risk devices may also be considered minimal risk studies and thus may be reviewed through the expedited review procedure established by the RSRB. FDA considers studies of all significant risk devices to present more than minimal risk; thus, RSRB review at a convened meeting is required for all studies involving significant risk devices. In considering whether a study should be approved, the RSRB will use the same criteria it would use in considering approval of any research involving an FDA-regulated product. In considering the risks of the study, the RSRB will not simply judge the increase in risk over standard treatment, but rather the risk of the procedure as a whole. The RSRB will consider the risks and benefits of the test medical device compared to the risks and benefits of alternative devices or procedures in deciding the approvability of a study.

Is a Certificate of Confidentiality Needed?

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) and other DHHS agencies to protect identifiable research information from forced disclosure. They may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. Certificates can be applied to biomedical, behavioral, clinical or other research. Certificates can be issued for non-federally funded research if the research poses the same involuntary disclosure concerns.

RSRB Standard Language for Certificate of Confidentiality:

To help us further protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, the investigators cannot be forced (for example, by court subpoena) to disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note, however, that if an insurer or employer learns about your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

When the study is NOT federally-funded include the following additional statement:

Having a Certificate of Confidentiality from DHHS does not mean DHHS or the US Government supports this research study.

To read more about certificates of confidentiality, click here:
<http://grants2.nih.gov/grants/policy/coc/>

Do any members of the study team have a conflict of interest with the proposed research?

An investigator is not permitted to conduct research in which he/she has a significant conflict of interest, as defined by University policy. To access the University's conflict of interest policy, click here:

<http://www.rochester.edu/ORPA/policies/index.html#Conflict%20of%20Interest%20and%20Misconduct>

NOTE: The RSRB discourages investigators from paying themselves to participate in their own research. Such payment is considered a conflict of interest.



Stop . . . and take an inventory

Pre-submission checklist

Does your activity. . .

- Involve human subjects?
- Involve research?
- Need review by the RSRB? By WIRB?
- Qualify for Just-in-Time review?
- Need approval by other UR Committees?
- Need off-site approval(s)?
- Require an IND or IDE?
- Require Data & Safety Monitoring?
- Need a Certificate of Confidentiality?

Have the Investigators/Study team. . .

- Received EPRP certification (minimal risk research)?
- Received HSPP certification (minimal risk and greater than minimal risk research)?

Do any of the members of the research team. . .

- Have a conflict of interest?

Questions?

Call the RSRB office at (585) 275-2398.

Writing the Research Protocol

To ensure an effective review, the RSRB must be provided with a research protocol (study plan) that contains certain critical elements of information. The protocol needs to address these areas in detail. For any questions concerning protocol preparation, call an RSRB Human Subjects Protection Specialist at (585) 275-2398. The Office for Human Subject Protection also has a web-based help module at: http://www.rochester.edu/ohsp/investigators/basic_guidelines.html

A protocol template can be found on the RSRB website:
<http://www.rochester.edu/rsrb/submission-documents/index.html>

For additional information on conducting clinical trials in accordance with Good Clinical Practice (GCP), please refer to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidance.
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>)

NOTES:

- A grant proposal *does not* substitute for the RSRB protocol/study plan. For studies supported by grants, submit a *separate protocol*, based on the guidelines provided below.
- Make sure to date *each version* of the protocol as it is revised. This step is crucial in keeping track of any modifications as the protocol proceeds through the review process.

I. OBJECTIVES AND BACKGROUND

- a) **Objectives:** state the specific scientific questions to be answered by the research. Meeting the objectives should be feasible with the predicted sample size of the study. (Note: if the sample size needs to be increased after approval, you must get RSRB approval before enrolling beyond the original number.) Include any hypotheses.
- b) **Background:** The background provides scientific justification of the objectives by summarizing the results of similar studies (information obtained in animal studies or pilot studies performed in humans, for example). Cite references to support justification for conducting the study.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

- a) **Eligibility Criteria:** List in clear detail the inclusion and exclusion criteria. Provide a sound scientific basis for every criterion defining the characteristics of the research population. These should be scientifically valid and help further define the subject population. Consider the following:
 - Subject population characteristics
 - Numbers of available and eligible subjects
 - Acceptable disease status/condition (concomitant illnesses)
 - Prior therapy (if any)
 - Enrollment in other research studies
 - Permitted or prohibited concurrent treatment
 - Time constraints for performance of pre-study (eligibility) tests
 - Ability of the subject to provide informed consent

NOTE: Enrolling a person who does not fit the inclusion criteria listed in the study plan is a protocol violation/deviation.

NOTE: The RSRB considers the inclusion and exclusion criteria as the specific scientific rationale supporting the enrollment of subjects. The data provided in these sections are **not** “estimates” or “ballpark figures.”

- b) **Number of subjects:** State the total number of subjects expected to participate. In the case of multi-center protocols (performance sites in addition to those over which the RSRB has jurisdiction), also include the overall total. If you are unsure of the exact number of subjects who will be recruited, it is permissible to use an approximation. Consider if the study population is of an appropriate size to achieve scientifically and statistically significant results.

NOTE: If your enrollment will exceed the number for which your project is approved, you must amend the protocol and obtain RSRB approval of this amendment before exceeding that number.

- c) **Sex of subjects:** Describe the intended male-female distribution of the subjects. If there are any sex-based enrollment restrictions, explain and justify the nature of these restriction(s). Equitable inclusion of both men and women in research is important to ensure that both receive an equal share of the benefits of research and that neither bears a disproportionate burden. Include both men and women unless there are appropriate scientific and/or medical reasons.

NOTE: Women of childbearing potential may not be routinely excluded from participating in research.

- d) **Age of subjects:** State the age range of the subjects, and provide the rationale for selecting this age range. Participation of adult subjects in research should not be age-restricted unless there is scientific and/or medical justification. Children should not be routinely excluded unless the research is not applicable to them or presents unacceptable risks. Specific RSRB approval must be obtained before enrolling children in research, and the protocol must describe the process for obtaining parental permission and age-appropriate assent of children.

NOTE: The age of majority in New York State is 18. Special considerations and regulations apply to research with children, so specific RSRB approval must be obtained before enrolling children in research.

- e) **Racial and Ethnic Origin:** Describe the intended racial and ethnic distribution of the subjects. If there are any enrollment restrictions based on race or ethnic origin, explain and justify the nature of these restrictions. Research should include sufficient enrollment of persons of diverse racial/ethnic backgrounds to ensure that the benefits and burdens of research participation are distributed in an equitable manner.
- f) **Vulnerable Subjects:** If vulnerable subjects (those who are susceptible to undue influence, with limited autonomy or those in subordinate positions) are included, provide justification.

NOTE: Children, pregnant women, the elderly, students, employees, fetuses, prisoners and persons with decisional incapacity are generally considered vulnerable subjects in need of greater protection. Address any recruitment issues/concerns regarding these subjects in the protocol/study plan.

III. METHODS AND PROCEDURES

- a) **Study Design** - For studies employing **drugs and/or devices**: List all drugs and/or devices that will be used for the study (whether for the research or as standard of care). For drugs, include:
- o Human toxicity
 - o Pharmaceutical data
 - o Administration route and dosage
 - o Storage and stability
 - o Supplier
 - o Investigational New Drug (IND number) or Investigational Device Exemption (IDE/510k number)
- Categorize and describe each segment or phase of the study, including screening procedures. Specify the duration of the subject's participation in the study (E.G., one visit? Three? Six months? Five years?). For studies involving a single interaction/event, indicate the anticipated time commitment. It may be helpful to include a study visit schedule in a table format.
 - Provide a detailed description of the study design – e.g., survey; randomized, double-blind, placebo-controlled; retrospective record/chart review. If the study uses an existing database, provide a description of the database. If applicable, indicate how subjects will be assigned to each group and describe the procedures and intervention/observation for each.
 - Thoroughly describe all examinations, blood tests (specify total amount of blood and number of draws), x-rays, surveys, behavioral measures (list each measure and briefly describe each tool), chart or record reviews or other procedures that will be used to obtain information about subjects. Describe these activities in a clear and logical sequence. Describe the timing of these events. **Identify which procedures are done for research purposes and which would occur regardless of the research** (i.e., standard of care, normal events, etc.). This information is often best presented as a "Table of Procedures."
 - List criteria for investigator-initiated subject removal from the research study. (Subjects may always withdraw for their own reasons.) Examples include:
 - o Inability to make study visits
 - o Unacceptable toxicity
 - o Progressive disease
 - o Inability to follow study directions
- b) **Data Monitoring**: For trials that involve interventions that entail potential risk to subjects, a data monitoring plan is required to protect subject safety and welfare. Provide a detailed description of the data monitoring plan (if a DSMB is to be used, describe its membership and function, frequency of review and stopping rules).

- c) **Statistical Analysis:** Provide a clear description of the statistical analysis to be used; remember that the sample size needs to be able to support the objectives. Suggested information for this section includes:

- A brief recap of study objectives
- The anticipated accrual rate and the accrual goal for the study
- The study design, including contingencies for early stopping
- A clear estimate of the sample size needed to address the major study objective(s), including the assumptions involved in the determination of power and tables of power under various alternatives
- The power of the study to address the other objective(s), the assumptions involved in the determination of power
- Planned statistical analysis of study data

NOTE: Consultation with a biostatistician to plan the statistical analysis is highly recommended, particularly for studies involving comparisons of treatments.

- d) **Reportable Events:** Clearly describe the criteria (what is to be reported), who will receive reports and the timeframe for reporting events. Note that not all adverse events are reported to the RSRB; only unanticipated problems with risks to subjects or others must be reported.
- e) **Data Storage and Confidentiality:** Describe where the research data will be stored during the study and how it will be secured. Steps to maintain confidentiality may include coding the data and choosing an appropriate and secure storage mechanism (e.g., encryption and password protection) that will prevent unauthorized access. State who will have access to the data. If data with subject identifiers will be released to others, specify the person(s) or agency to whom the information will be released and the purpose of the release (e.g., routine verification of case report forms). Remember to consider HIPAA regulations regarding protected health information (PHI).

IV. RISK/BENEFIT ASSESSMENT

- a) **Risk Category:** A risk is a potential harm associated with the research that a reasonable person would likely consider injurious or uncomfortable. Under the federal regulations, research is categorized as either “greater than minimal risk” or minimal risk.” **Minimal Risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- b) **Potential Risk:** Describe the potential risks associated with the study. For studies involving medications, this includes a clear explanation of adverse effects, precautions and contraindications.

NOTE: Risks to research participation may not be just physical – consider possible psychological, sociological, economic and legal risks as well.

- c) **Protection Against Risks:** Describe how the study design and procedures will prevent and/or minimize any potential risks or discomfort. Potential risks and discomforts must be minimized to the greatest extent possible by using procedures such as appropriate training of personnel, monitoring, withdrawal of the subject upon

evidence of difficulty or adverse event; referral for treatment, counseling or other necessary follow-up. State who will pay for treatment of adverse events or follow-up.

- d) **Potential Benefits to the Subjects:** Describe the potential benefit(s), if any, for subjects participating in the research. If there are no anticipated direct benefits to subjects, say so. (Many research projects are justified by the potential benefit to society/science, emphasizing the need for sound study design.)

NOTE: Payment to subjects is not considered a benefit of research; it is a recruitment inducement.

- e) **Alternatives to Participation:** Describe alternative courses of action (including any less risky than the study procedures) which are available should the subject elect not to participate in the study. If the subjects are students who will receive academic credit for participation, describe the alternatives available to earn equivalent academic credit. Academic alternatives must be approximately equal in time and effort required.

V. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

- a) **Method of Subject Identification and Recruitment:** Describe the method(s) that will be employed to identify and recruit prospective subjects. The identification and recruitment of subjects must protect individual's privacy and be free of undue influence. If access to medical or other private records is necessary to identify subjects, indicate whether the research team has routine access to these records. **Only investigators with routine access to their prospective subjects (or subject records) may recruit these individuals directly.** Other investigators must work through the person/institution with legitimate access (e.g., using referral letters, general announcements, etc.).

Describe explicitly how subjects will be recruited for this research, e.g., media advertisements (TV, radio or newspaper), recruitment letters, posters, brochures recruiting services/web sites, or direct contact. Initial contact with potential subjects must be made by someone who has routine access to these individuals (i.e., no "cold calls").

NOTE: Recruitment of an investigator's own students, employees or patients is considered *potentially coercive*. Steps taken to minimize undue influence should be included in the study plan/protocol.

- b) **Process of Consent:** Describe who will obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision-making by the subject/subject's authorized representative without any element of coercion or undue influence. Potential subjects should be given ample time to consider participation (not approached on the day the intervention is to take place, e.g.). If used, auditor/witness and translator roles should be described in this section.
- **Screening:** Indicate whether any screening procedures are needed to determine eligibility for participation. If so, screening consent procedures must be addressed. Indicate if a screening consent form will be included, or if a waiver of consent or a waiver of documentation of consent (e.g., telephone screening

with verbal consent that does not obtain the subject's signature) will be requested. (Note: Unless permission is obtained, identifiable data on individuals who do not pass the screening or who do not give consent to the study cannot be kept in study records.)

- **Subject Capacity:** If not all subjects will have the capacity to give informed consent, describe how capacity will be assessed, and who will conduct the assessment. Describe the anticipated degree of impairment relative to the subjects' ability to consent to participate in research. Describe procedures to reassess capacity in long-term studies.
- **Subject/Representative Comprehension:** All investigators have a legal and ethical obligation to ensure that prospective subjects/subjects' representatives have sufficient knowledge and comprehension of the elements of consent to enable them to make an informed and enlightened decision whether or not to participate or allow participation in research. In this section, describe how the subject's/authorized representative's understanding of the information presented will be determined. Include an adequate plan to assure an acceptable level of comprehension before consent is obtained. If children and/or decisionally impaired adults will be subjects, include a specific plan to assess comprehension during assent (the child's agreement).

For more information on the enrollment of adults lacking decisional capacity, see [Appendix 1](#).

- **Debriefing Procedures:** In psychological studies where some information will be purposely withheld from the subject (i.e., deception), state the information to be withheld, justify this non-disclosure and describe the post-study debriefing of the subject, i.e., how the subject will be informed of the missing information and whether data can be withdrawn after debriefing.

For more information on studies involving deception, see "Waivers of Consent for Deception Research" below.

- **Consent Forms:** Consult the RSRB consent form guidelines for specific sections required for consent documents. The first page of the consent form must be printed on the department's or University's letterhead.
 - **Documentation of Consent:** The PI is responsible for ensuring that valid consent is obtained and documented by HSPP- or EPRP-trained study team members for all subjects. If not already addressed in item b) above (Process of Consent), specifically describe how consent will be documented and how/where documentation (i.e., the original signed copies) will be stored.
- c) **Costs to the Subject:** Describe and justify any costs that the subject will incur as a result of participating in the study. Clarify who will pay for procedures associated with the study (e.g., agency grant vs. departmental funds). Normally, subjects should not have to pay for research procedures that do not yield direct benefit. No charge may be made to subjects if the costs are covered by a grant, contract, or other payment method. Generally, no charge is permitted by FDA for unapproved investigational drugs and devices.
- d) **Payment for Participation:** Describe any reimbursements or payments such as cash, coupons or extra class credit that the subjects will receive for participation. List the prerequisite condition(s) that must be fulfilled by subjects to receive these

payments. The amount must be justified and not constitute undue inducement of the subject to participate in the research or to continue beyond a point that they would have otherwise withdrawn.

Points to keep in mind:

- The amount and schedule of all payments need to be presented to the RSRB at the time of initial review.
- The RSRB will review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive or presents undue influence.
- Any amount paid as a bonus for completion must be reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
- All information concerning payment, including the amount and schedule of payments, must be set forth in the consent form.
- Payment for participation in a clinical trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once (if) it has been approved for marketing.

NOTE: The RSRB requires a prorated system for financial payments. This means that payments are accrued as the study progresses and that subjects do not have to complete the entire study to be eligible to receive a payment. This is to protect the subject's right to withdraw without penalty.

VI. REFERENCES

All references must be complete, numbered and listed in the order that they appear in the protocol.

VII. APPENDICES

Include in this section any charts or special forms referenced in the body of the protocol (e.g., toxicity criteria, performance status scales, measures [other than standard tests], etc.).



Stop . . . and take an inventory

Protocol Checklist

Is the protocol. . .

- Dated? Paginated (with version number or date)?
- A stand-alone document, separate from the grant application?

Does the protocol. . .

- Include all pertinent elements?
- Differentiate research from non-research activities?
- Need a data monitoring plan?
- Have sufficient sample size to address the objectives?
- Address the risks of the research?
- Involve deception? (applicable only to minimal risk studies)

Do the subjects. . .

- Have capacity to consent?
- Represent any vulnerable populations?

Does the investigator. . .

- Have routine, legitimate access to potential subjects (i.e., can he/she recruit subjects directly)?

Categories of Research and RSRB Review

Research involving vulnerable populations

Individuals with limited autonomy or those in subordinate positions are considered “vulnerable subjects” in need of greater protection (i.e., to prevent inappropriate enrollment). Vulnerable subjects may include children, pregnant women, the elderly, students, employees, fetuses, prisoners, the economically or educationally disadvantaged and persons with decisional incapacity.

The following descriptions are provided as additional considerations for investigators who plan to conduct research with vulnerable populations.

a) Research Involving Children

Children are considered a vulnerable research population because their intellectual and emotional capacities are limited. Where appropriate, studies should be conducted first in adult, then in older children prior to involving younger children. According to New York State law, children are those persons under the age of 18 years. Children, by definition, cannot give legal “consent.” Therefore, a combination of assent (agreement) of the child-subject and permission of the parent(s) is used as a safeguard.

The federal regulations specify **four categories of acceptable research with children:**

- 1) **Research involving no more than minimal risk** (45 CFR 46.404 and 21 CFR 50.51), if:
 - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. (The RSRB may find that the permission of one parent/guardian is sufficient.)

- 2) **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects** (45 CFR 46.405 and 21 CFR 50.52), if:
 - The risk is justified by the anticipated benefit to the participants.
 - The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternatives, and
 - Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. (The RSRB may find that the permission of one parent/guardian is sufficient.)

- 3) **Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition** (45 CFR 46.406 and 21 CFR 50.53), if:
 - The risk represents a minor increase over minimal risk;
 - The intervention or procedure presents experiences to the children that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;
 - The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and

- Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. (The permission of both parents/guardians is required unless one parent is deceased, unknown, incapacitated, or when only one parent has legal custody of the child.)
- 4) **Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children** (45 CFR 46.407 and 21 CFR 50.54) if:
- The RSRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, and
 - Either the RSRB (for non-federally funded studies) or OHRP (for federally funded studies), conducts further consultation with experts in pertinent disciplines (e.g., science, medicine, education, ethics and law), and finds that either:
 - the research actually satisfies one of the categories noted above **or**
 - confirmation that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children; the research will be conducted according to sound ethical principles; **and** adequate provisions are made for soliciting the assent of children and the permission of their parents/guardians. (The permission of both parents/guardians is required unless one parent is deceased, unknown, incapacitated, or when only one parent has legal care and custody of the child.)

b) Research Involving Pregnant Women and Fetuses

Federal regulations (45 CFR 46.206-209) require special protections for women and fetuses involved in federally sponsored research. The University also uses these regulations as guidance for non-federal, non-medical research. The regulatory protections are summarized below:

- Appropriate studies conducted on animals and non-pregnant women have provided data for assessing potential risks.
- Risks and prospects of benefit to the fetus and mother (separately or together) and the purpose of the research have been determined.
- Any risk is the least possible for achieving the objectives of the research.
- Based on the risks and prospect of benefit to the woman and fetus, adequate provision is made for obtaining consent. Consent may be obtained solely from the mother, unless the research is only for the benefit of the fetus, in which case consent must be obtained from both the mother and father.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy; and individuals engaged in the research will not have a part in decisions to terminate a pregnancy or determine the viability of a neonate.

c) Research Directed Toward Pregnant Women as Subjects (45 CFR 46.207)

Pregnant women may be involved as research subjects if:

- The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or
- The risk to the fetus is minimal.

In either case, research activity may be conducted only if the mother and father are legally competent and have given their consent after having been informed about the possible impact on the fetus.

The father's consent is not needed if: 1) the purpose of the activity is to meet the health needs of the mother; 2) his identity or whereabouts cannot reasonably be ascertained; 3) he is not reasonably available or 4) the pregnancy resulted from rape.

d) Research involving nonviable neonates and neonates of uncertain viability (45 CFR 46.209)

(Note: the federal regulations use a definition for "neonate" that is at variance with common terminology – for purposes of the regulation, "neonate" means a newborn before the viability determination.)

Until it has been ascertained whether or not it is viable, a fetus *ex utero* may not be involved as a research subject unless:

- There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge that cannot be obtained by other means, or
- The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

No nonviable fetus may be involved as a research subject unless:

- Vital functions of the fetus will not be artificially maintained,
- Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and
- The purpose of the activity is the development of important biomedical knowledge that cannot be obtained by other means.

If the fetus *ex utero* is found to be viable, it may be included as a research subject only within the requirements noted here.

Research activity may be conducted under this section only if the mother and father are legally competent and have given their consent after having been informed about the possible impact on the fetus.

The father's consent is not needed if: 1) the purpose of the activity is to meet the health needs of the mother; 2) his identity or whereabouts cannot reasonably be ascertained; 3) he is not reasonably available or 4) the pregnancy resulted from rape.

e) Research involving the dead fetus, fetal material or the placenta (45 CFR 46.210)

Activities involving the dead fetus, macerated fetal material or cells, tissue or organs excised from a dead fetus may be conducted only in accordance with applicable State or local laws regarding such activities and federal policy on fetal tissue research.

f) Research involving prisoners (45 CFR 46.302-306)

The federal regulations require additional safeguards for the protection of prisoners, who, because of their incarceration, may be under constraints that could affect their ability to make a truly voluntary and uncoerced decision regarding participation in research.

NOTE: A “**prisoner**” means any individual involuntarily confined or detained in a penal institution, including: individuals sentenced to such an institution under a criminal or civil statute; individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.

For federally funded research, the RSRB must apply these regulations to individuals who are prisoners at the outset of the study, or who *become incarcerated after the study begins*.

The RSRB may permit research with prisoners if it initially finds:

- Any possible advantages accruing to the prisoner through participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that the ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
- The information is presented in language understandable to the participant population.
- Adequate assurance exists that parole boards will not take into account a prisoner’s participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
- Adequate provision has been made for follow-up examination or care, taking into account the varying lengths of individual prisoners’ sentence, and for informing subjects of this fact.

Permissible biomedical or behavioral research involving prisoners:

- Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

NOTE: In research with prisoners, minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy, non-incarcerated persons.

- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis, which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults).
- Research on both innovative and accepted practices that have the intent and reasonable probability of improving the health or well-being of the subject.
- Research that involves epidemiologic studies for which the sole purposes of the research are one of the following:
 - To describe the prevalence or incidence of a disease by identifying all cases.
 - To study potential risk factor associations for a disease.
 - and**
 - The research presents no more than minimal risk and no more than inconvenience to the prisoner participants.
 - Prisoners are not a particular focus of the research.

Additional Research Considerations

1) Research Involving Genetic Testing

The State of New York has adopted additional protections for individuals participating in research regarding genetic testing, based on the following definitions:

- **Genetic test:** any laboratory test of human DNA, chromosomes, genes or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis. A genetic test does not include any test of blood or other medically prescribed test in routine use that has been or may be hereafter found to be associated with a genetic variation, unless conducted purposely to identify such genetic variation.
- **Genetic predisposition** means the presence of a variation in the composition of the genes of an individual or an individual's family member that is scientifically or medically identifiable and that is determined to be associated with an increased statistical risk of being expressed as either a physical or mental disease or disability in the individual or having offspring with a genetically influenced disease, but which has not resulted in any symptoms of such disease or disorder.

NOTE: under this law, the RSRB does not consider "genetic testing" to include studies of gene expression.

Specific provisions are required in consent forms used for studies involving genetic testing. See the sample genetic testing consent form language.

2) Research Involving HIV Testing and Subjects with AIDS

Policy on Informing Subjects about HIV Serostatus: When HIV testing is conducted as part of a research project on individuals whose test results are associated with personal identifiers, such individuals must be informed of their own test results and provided with the opportunity to receive appropriate counseling. Individuals may not be given the option "not to know" the result, either at the time of consenting to be tested or thereafter. This policy does not apply to testing situations in which subjects consent to be tested but specimen results cannot be linked to individual subjects.

New York State has enacted a law governing HIV testing and the release of confidential HIV/AIDS information [Public Health Law (2780ff)]. The law defines an HIV-related test to mean any laboratory test or series of tests for any virus, antibody, antigen or etiologic agent whatsoever thought to cause or to indicate the presence of AIDS.

No HIV-related test may be performed without the written, informed consent of the subject and without the subject having been provided pre-test counseling as mandated by New York State law. Informed consent and pre-test counseling shall consist of:

- An explanation of the test, including its purpose, the meaning of its results, and the benefits of early diagnosis and medical intervention; and
- An explanation of the procedures to be followed, including that the test is voluntary, that consent may be withdrawn at any time, and a statement advising the subject that anonymous testing is available; and
- An explanation of the confidentiality protections afforded confidential HIV-related information under New York State Law, including the circumstances under which and classes of persons to whom disclosure of such information may be required or authorized.
- An explanation of the nature of AIDS and HIV-related illness, information about discrimination problems that disclosure of the test result could cause and legal protections against such discrimination, and information about behavior known to pose risks for transmission and contraction of HIV infection.

At the time of communicating the test result to the subject, the person ordering the performance of the test must provide the subject with mandated post-test counseling. Post-test counseling shall consist of information regarding:

- Coping with the emotional consequences of learning the result;
- The discrimination problems that disclosure of the result could cause;
- Changes in behavior to prevent transmission or contraction of HIV infection;
- Available medical treatments, and
- The test subject's need to notify his or her contacts.

The requirements for pre-test and post-test counseling do not apply in the context of a research protocol if the testing is performed in such a manner that the identity of the test subject is not known and may not be retrieved by the researcher.

With respect to the release or disclosure of confidential HIV-related information, with limited exceptions, New York State law prohibits the release of confidential HIV/AIDS information without the written consent of the subject. Moreover, the law requires that a special HIV/AIDS release form be utilized. An ordinary release of medical information/records form is not sufficient for the release of confidential HIV/AIDS information.

The law defines confidential HIV/AIDS related information as: any information indicating that "an individual has been the subject of an HIV test, or has HIV infection, HIV-related illness or AIDS, or information which identifies or reasonably could identify an individual as having one or more of such conditions, including information pertaining to such individual's contacts." Any unauthorized release confidential AIDS/HIV information is a crime (misdemeanor).

Any authorized disclosure of HIV/AIDS information must be accompanied or followed within 10 days by the following written statements prohibiting further redisclosure:

This information has been disclosed to you from confidential records which are protected by State law. State law prohibits you from making any further disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law. Any unauthorized further disclosure in violation of State law may result in a fine or jail sentence or both. A general authorization for the release of medical or other information is not sufficient authorization for further disclosure.

New York State law also sets forth a required process for contact notification where the physician determines that disclosure is medically appropriate and there is a significant risk of infection to the contact.

Exceptions to Informing Subjects about HIV Serostatus:

- **Pertaining to an Individual:** Where there are compelling and immediate reasons that justify not informing a particular individual that he or she is seropositive, e.g., indication that an individual would attempt suicide, the particular individual need not be informed of HIV test results. When this exception is made to the policy of informing individuals, the details of the exception shall be documented by the principal investigator, who then must promptly report the exception to the RSRB.
- **Pertaining to Foreign Sites:** Research activities conducted at foreign sites should be carefully evaluated to account for cultural norms, the health resource capabilities and official health policies of the host country. The RSRB will consider if any modification to the policy is significantly justified by the risk/benefit evaluation of the research. The RSRB may seek expert advice, e.g., local public health experts, in evaluation of these projects.

Counseling: Any person tested for HIV infection should receive the results of their tests and counseling in a timely fashion from an individual qualified to provide test counseling and partner notification services (not necessarily an individual on the research team).

Confidentiality: Perhaps the most sensitive aspect of AIDS research from the perspective of the rights and welfare of the subjects is the matter of confidentiality. 45 CFR 46.116(1)(5) and 21 CFR 50.25(a)(5) require a statement of the extent to which confidentiality of records identifying the subject will be maintained.

Improper disclosure could have the most serious consequences for research participants, by threatening family relationships, job security, employability, or ability to obtain credit or insurance. In light of these risks, special precautions should be taken to preserve confidentiality, and potential subjects should be advised with care of the limits of that confidentiality, so they can make thoughtful, informed decisions, in light of their own circumstances, as to whether to participate.

Each study is to be designed with administrative, management and technical safeguards to control authorized use and disclosure of information and to protect against unauthorized disclosure. Where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who

elected not to participate. Participants must be given a fair, clear explanation of how information about them will be handled.

As a general principle, information is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take account of the possibility of review of records by the funding agency, and by FDA officials if the research is subject to FDA regulations.

The RSRB will consider what information will be recorded in the subjects' medical records, and may wish to minimize the recording of data from AIDS-related studies in the medical records. Some states or other jurisdictions may require AIDS to be reported and may require follow-up. Participation in research does not exempt compliance with those laws, but potential study participants must be fully informed of laws requiring disclosure of information before they volunteer for the studies.

3) Research Databases

Federal regulations direct the RSRB to review activities in which research data are obtained from or used to establish databases.

Under University policy, clinical and mixed-use databases (those used to maintain both clinical and research data) do not require review and approval by the RSRB. However, the use of these data in support of a research activity (e.g., involving retrospective record review) requires RSRB review and approval.

A database established *solely* for research purposes requires RSRB review and approval. Use of these data in support of additional research activity likewise requires separate review and approval by the RSRB. When composing a research database protocol, consider the following:

- Purpose
 - What is the purpose of the database?
- Information in the database
 - What type of data will be collected?
 - What identifiers will be collected?
- Maintenance
 - Where and how the database will be maintained?
 - Who will be responsible for maintaining it and assuring the quality of the data?
 - How long will the database be in place? Indefinitely?
 - Under what circumstances will data be destroyed? And if destroyed, how will it be destroyed?
 - How will confidentiality be assured if identifiers (e.g. medical record number, specimen numbers, DOB) are collected?
- Release of Data to Researchers
 - Who will be eligible to request data from the database?
 - Who will be responsible for providing data to researchers?
 - How will that person assure that RSRB review has been completed for the project for which data is requested?

4) Coordination Centers

Federal guidelines direct the RSRB to review coordinating center activities (i.e., administrative processes and responsibility) when the University is coordinating multi-site collaborative research. The RSRB conducts an expedited review of a master protocol and sample consent

form prior to their distribution to participating sites. In addition, the RSRB will determine and document that the following mechanisms are in place:

- Management, data analysis, and data safety and monitoring systems are adequate, given the nature of the research involved
- Sample protocols and informed consent documents are developed and distributed to each collaborating institution
- Each collaborating institution holds an applicable Federalwide assurance
- Each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects
- Any substantive modification by the collaborating institution to sample consent language related to risks or alternative procedures is appropriately justified, and;
- Informed consent is obtained from each subject in compliance with HHS or FDA regulations.

NOTE: The Coordination Center study is separate from the enrolling-site study.

Monitoring of Coordination Centers

Along with the continuing review report (which includes the enrollment figures for all sites), the coordinating center should provide a summary/ analysis of all events (AEs, SAEs, UPIRTSOs, etc.) reported by the enrolling study sites. The RSRB may request an audit of the coordinating center's files comparing the regulatory document tracking spreadsheet to the enrolling sites' IRB correspondence files. Amendments (requests for changes) must be submitted to the RSRB for review and approval prior to implementation by enrolling sites; amendments should be numbered sequentially and identified by version dates.

Writing a Coordination Center Protocol

For a coordinating center protocol, summarize the preparation and implementation of the research project/program. Describe the following:

Pre-study Responsibilities (for example)

- Drafting and refinement of the study protocol(s) and consent form(s)
- Documenting OHRP-approved assurances for each site
- Overseeing development/design of data collection forms
- Establishing subcontracts with investigative sites and other research units.
- Documenting that the protocol is reviewed and approved by the IRB at the enrolling/collaborating sites prior to enrollment of subjects.

Responsibilities During the Conduct of the Study (for example)

- Updating the protocol and operations manual (if applicable) as needed
- Assuring that informed consent is obtained from each subject in compliance with regulations
- Updating the regulatory files for the study overall, as well as documenting the timely renewals of IRB approvals at the sites.
- Overseeing real-time monitoring of enrollment
- Conveying information to the IRBs, sponsors and sites on a regular basis.
- Fielding and replying to site protocol inquires.

Protocol Elements (include all tasks required for study implementation at the sites)

- Describe how the coordinating center will monitor each site. Please refer to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidance for additional information regarding monitoring of clinical trials (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>)
- Describe the enrollment process. Clarify who is responsible for the registration/enrollment of subjects at each site (the coordinating center or the site).
- Describe the coordinating center's procedures for study closures and early site terminations.
- Describe how the coordination center monitors data for enrollment, withdrawals and reportable events.
- Explain how confidentiality of data will be maintained by each site and by the coordinating center. Include the following:
 - Where the research data will be stored during the study and how it will be secured.
 - Methods to prevent unauthorized access to data.
 - Who will have access to the data?
 - If data with subject identifiers will be released, specify the person(s) or agency(s) to whom the information will be released and the purpose of the release.
- Explain specimen management (if applicable). Describe the following and include in both the model consent form and contracts:
 - What specimens will be collected?
 - How the samples will be used/stored?
 - Where will the specimens be stored?
 - Who has ownership of the specimens?
 - How are specimens transported to a central repository? (if applicable)
 - Explain if/how the samples will be used for current study or future use. (Include that subjects will be allowed to agree or disagree to the future usage/storage of the collected samples.)
- Describe how the coordination center will do the statistical analysis.
- Describe how the coordination center will do the safety monitoring.
- Clarify if a data safety monitoring board will be used. Provide a detailed description of its operation (i.e. the membership, function, frequency of review, reporting format/schedule and stopping rules).

Sample Protocol and Model Informed Consent

Protocols and model consent forms must be approved by the RSRB prior to distribution to collaborating institutions. The RSRB will provide a stamped, approved final model consent form template that the coordination center maintains in its files but does not distribute to performance sites. "Model Consent" will be indicated on the approval stamp. The unstamped approved version will be distributed to performance sites.

When the sample model consent is sent to the study sites, a transmittal letter should include the following information:

- Local IRB changes to the sample consent are permissible and editorial changes to the consent may be made as long as they do not change the information or intent. Any substantive modification of the sample consent information related to risks or alternative procedures must be appropriately justified to the coordination center.
- Any changes requested by the sites must be reviewed/approved by the coordination center and all IRB approved consents must be received by the coordination center prior to subject enrollment at the site(s).

Regulatory Document Tracking Spreadsheet (suggested)

The Regulatory Document Tracking Spreadsheet should include the following:

- Site Number
- Site Name
- Enrolling Investigator
- Assurance number (FWA)
- Site IRB Approval Protocol Date
- Site IRB Approval Consent Date

Levels of RSRB Review

The type of RSRB review a study receives depends on the risks posed to subjects by the research. These risks include the probability and severity of possible harm or discomfort to the subjects' physical, psychological, social, legal or economic welfare. Research is reviewed by the RSRB at convened meetings unless it involves minimal risk and qualifies for expedited review or exempt status. Even if a study qualifies for exemption or expedited review, the RSRB may choose to conduct its review at a convened meeting. Generally, this occurs when a study presents a unique situation, or extremely novel approaches and experiences for research subjects.

NOTE: Per University policy, all studies involving gene transfer and/or genetic testing are reviewed at convened meetings.

Exempt Activities / Research (45 CFR 46.101(b))

Activities in which the only involvement of human subjects is in one or more of the six numbered categories below are exempt from RSRB convened meeting review and from other requirements of federal regulations. The RSRB office determines whether studies qualify for exemption from continuing review.

What does it mean if my study is "exempt"?

Unlike other types of research, which require continuing review by the RSRB, exempt studies are generally reviewed only once – to determine and confirm the exemption. The RSRB office does review modifications to these studies, to ensure that the exemption still applies.

If, after reviewing the exemption application, the RSRB office determines that a higher degree of risk may be involved, or if there are questions about human subject protection, the investigator may be requested to submit such proposals for expedited or convened meeting review.

All exempt research involving human subjects must have adequate subject privacy protections and maintain an adequate standard of informed consent and confidentiality of research data. In some exempt research projects, written informed consent should be obtained and documented, even if not required by the human subject regulations. An example would be obtaining the written consent of parents for research involving educational strategies for their children.

Before considering the exemption categories, ask whether your proposal involves human subjects or research:

- (A) **Exemption Category A - Activities Being Conducted Are Not Research:** The activity is not regulated by the FDA and there is no systematic investigation (no study plan) and the information collected will not be used to develop or contribute to generalizable knowledge (i.e., the activity's conclusions are NOT intended to be extended beyond the sample or internal program) other than as a report of the activity (i.e., it will not be externally disseminated for scientific purposes). For example, the project is an evaluation for a specific department, agency, company, or institution and the results will not be published or otherwise disseminated

NOTE: In general, the RSRB does not consider case reports or small case series without study plans/protocols as research.

- (B) **Exemption Category B - Research Does Not Involve Human Subjects:** The study is not regulated by the FDA and either:
- a) does not involve living individuals or data collected from living individuals
- OR
- b) involves the use of tissues or data that were collected for some other purpose by someone other than the investigator and are not linked to the individual by any identifiers. The research data/tissues must be anonymous (i.e., devoid of *any* information identifying the individual) when the investigator receives the data/tissues. The investigator may not receive data/tissues that contain any direct or indirect identifiers, including any codes that can be linked by the investigator to the individual data/tissues.

The activity may use for example, autopsy material or review of records of deceased individuals or specimens obtained in clinical practice or some other research project.

NOTE: The exemption categories below **do not** apply to research involving prisoners. Category 2 **does not** apply to research with children.

The following categories of exemption are allowed by the University (per 45 CFR 46.101(b), 45 CFR 46.201(b), 45 CFR 46.301(a), 45 CFR 46.401(b) and 21 CFR 56.104):

- (1) **Research conducted in established or commonly accepted educational settings, involving normal educational practices**, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
 - The research does not involve prisoners as participants.
 - The research must not be FDA-regulated.
 - **“Commonly accepted educational settings”** include the typical classroom setting of schools, colleges, etc. but also includes other routine training sites such as health education classes, job training sites etc.
- (2) **Survey, Interviews, Standardized Educational Tests, and Observation of Public Behavior** - Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, *unless*: information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and any disclosure of the 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.

- The research does not involve prisoners as participants.
- The research is not FDA-regulated.
- “Public behavior” is behavior generally open to view by any member of a community and would not involve any special permission to observe, such as, at a park, in a mall, at a movie theater, etc. Therefore, what occurs in a classroom, for example, would not be considered observation of public behavior.

NOTE: When a study in this category uses subjects who are **children**, only research involving observation of public behavior when the investigator(s) does not participate in the activities being observed is exempt.

- (3) **Surveys, Interviews and Observation of Public Behavior of Elected or Appointed Public Officials** - 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 (2) above, if: the human subjects are elected or appointed public officials or candidates for public office; or Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter (e.g., some DEA research).
- The research does not involve prisoners as participants.
 - The research must not be FDA-regulated.
- (4) **Secondary Use of Pre-Existing Data** - 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.
- The research does not involve prisoners as participants.
 - The research must not be FDA-regulated.
 - The materials to review must exist at the time the research is proposed (i.e., submitted to the RSRB).
 - To confirm that the study is retrospective and de-identified (void of the 18 HIPAA identifiers), the RSRB will review a copy of the data collection sheet and the start/end dates of original data collection.
- (5) **Evaluation of Public Benefit or Service Program** - Research and demonstration projects which are conducted by or subject to the approval of the federal government, and which are designed to study, evaluate, or otherwise examine: public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs.

Note: This exemption category generally refers to research commissioned by federal statute or legislative action.

- The research does not involve prisoners as participants.
- The research must not be FDA-regulated.
- The research must be conducted pursuant to specific federal statutory authority.
- The research must have no statutory requirements for RSRB review.
- The research must not involve significant physical invasions or intrusions upon the privacy interests of participants.

- (6) **Taste and Food Quality Evaluation** - Taste and food quality evaluation and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the federal government.

- The research does not involve prisoners as participants.

NOTE: If your study fits one of the exemption categories noted above, answer “yes” to question 9 in the RSRB’s online submission system (“Do you think this study may qualify as exempt under one of the federally recognized exemptions?”). This will enable you to categorize your study by its specific exemption.

Expedited Review – 45 CFR 46.110

Expedited review is performed by the RSRB chair or by an experienced RSRB member (or alternate) designated by the chair.

NOTE: Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

General Requirements for all Expedited Review Categories:

- Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories below may be reviewed by the RSRB through an expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- The categories apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified research involving human subjects.
- Standard requirements apply for informed consent (or its waiver, alteration, or exception).

NOTE: Research on procedures involving greater than minimal risk– **even if routinely conducted as standard of care** – do not qualify for expedited review.

Expedited Research Categories:

- (1) Clinical studies of drugs and devices only when condition (a) or (b) is met:
 - (a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required.

NOTE: Research on marketed drugs that increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

- (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period, and collection may not occur more frequently than 2 times per week; or
 - (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period, and collection may not occur more frequently than 2 times per week.
- (3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
- (4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

- (5) Research involving materials (data, documents, records or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects.)
- (6) Collection of data from voice, video, digital or image recordings made for research purposes.
- (7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: some research in this category may be exempt from the HHS regulations for the protection of human subjects.)
- (8) Continuing review of research previously approved by the convened board, as follows:
(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.
- (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 RSRB also conducts expedited review of the following studies, **none of which involve enrollment of human subjects**:

- **Umbrella studies** – grants and program projects that provide for the funding or oversight of studies that will involve human subjects. Individual studies covered under the umbrella undergo specific RSRB review appropriate to the risk involved.
- **Multi-Site Coordination Centers** - studies in which a University investigator provides administrative oversight for research conducted at one or more non-UR sites.
- **Concept studies** - An idea (concept) for a study submitted to the RSRB (usually as a grant requirement) prior to completion of the final protocol. Subject enrollment is not permitted until the RSRB's subsequent review and approval of the final protocol and consent form.

Review at Convened Meetings

Research that presents greater than minimal risk to subjects, or that does not qualify for exemption or expedited review, requires review at a convened meeting of the RSRB. Phase 1-4 drug studies and those involving the use of devices posing significant risk are examples of studies that would be included in this category.

The clinical investigation of drugs is generally divided into these four phases:

- **Phase 1:** includes initial testing of an investigational new drug with humans. These studies (usually conducted in healthy volunteers) are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses and, if possible to gain early evidence on effectiveness. These studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. The assessment of safety and documentation of adverse events is of primary importance. Some Phase 1 studies may be done to establish a dose (e.g., MTD) and/or schedule of an agent(s).
- **Phase 2:** includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication(s) in patients with the disease or condition. This phase also helps determine the common short-term side effects and risks associated with the drug.
- **Phase 3:** intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the product labeling.
- **Phase 4:** "post-marketing" studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies may include, but are not limited to, evaluating different dosages or schedules of administration, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

As noted earlier, under some circumstances, the RSRB may also choose to review minimal risk proposals at a convened meeting.

Submitting Studies to the RSRB

The RSRB office conducts an initial screening of all research proposals submitted to ensure that the applications are complete. Investigators are notified if submissions are incomplete, require additional information or need clarification.

The RSRB employs an [online protocol submission system](#), which enables investigators to track their studies throughout the review process. The system permits online submission of any electronically generated proposal documents, including the protocol, test forms/measures, consent form(s), recruitment materials, grant application, and University committee and external site approvals.

The goal of the online system is to help streamline the process of submitting and tracking research applications. Investigators can submit the following components online: new application, amendment, progress report and reportable events.

To access the online submission system, click here: <http://rsrb01.urmc.rochester.edu>

New Applications

Regardless of the level of review required, the RSRB requires submission of the following:

- A research protocol/study plan (reference "Writing the Research Protocol")

- If the proposal is federally or foundation-funded, a copy of the **entire** grant
- The consent/assent form(s) and all recruitment materials, including flyers, posters, newspaper ads, television/radio scripts, letters to prospective participants
- Measures used to collect study information (e.g., surveys, questionnaires, data collection sheets)
- If appropriate, supporting approvals from non-UR sites where the research will be conducted and UR committees (typically online)

Research Exempt from Continuing Review

The application will be reviewed by an RSRB specialist to determine whether or not the proposed research meets one or more exemption categories. If the proposal qualifies for exemption, you will receive written confirmation. If the proposal does not qualify for exempt status, you will receive a notification to that effect, with options to facilitate further review (e.g., submission for expedited review).

Reminders regarding exemption requests:

- If you are requesting an exemption for *research involving pre-existing data/specimens*, the information/materials collected MUST be both pre-existing and anonymous. This means:
 - The data/specimens must be ON THE SHELF at the time the exemption request is submitted to the RSRB. For example: If you submitted your study on 10/1/09, data/specimens collected up to 9/30/09 are considered pre-existing. Data/specimens collected *after* 10/1/09 are not.
 - The data/specimens must not contain any identifiers linking them to the subject. This means, no initials, code numbers, medical record numbers or encrypted identifiers
- If you are requesting an exemption for research involving surveys or interviews:
 - You may only enroll adults (i.e., subjects 18 years of age and older).
 - If the survey/interview involves the collection of “sensitive” information (i.e., data that may put the subject at risk of criminal or civil liability, or be damaging to the subject’s financial standing, employability or reputation), identifiers CANNOT be included.
 - If the survey/interview involves the collection of “non-sensitive” data, information identifying the subjects can be included.

Remember that HIPAA regulations concerning protected health information may apply to exempt studies.

Once a proposal is determined to be exempt, no further RSRB action or oversight is required, as long as the study is not modified. However, you must inform the RSRB of any modifications – e.g., addition of research procedures or new survey forms, study measures, etc. – so a decision can be made whether reclassification of the research (into the expedited or convened meeting category) is required.

Expedited Review

Complete applications are reviewed by an RSRB specialist and one or more RSRB members. In most cases, approval for minimal risk research will be granted for one year. All expedited approvals are reported to the full RSRB. If, in the rare case that the RSRB subsequently determines that the study requires convened meeting review, the Principal Investigator will be

notified and approval will be temporarily suspended until the convened meeting review process is complete.

Reminders regarding studies submitted for expedited review:

- The level of risk posed by a research procedure must be considered no greater than “minimal” for a study to qualify for expedited review – not the incremental risk posed in comparison to standard of care procedures.

Review at a Convened Meeting

The application will be reviewed by an RSRB specialist to determine whether or not the proposed research must be reviewed at a convened meeting and if so if all the information is complete and ready for the board. After the meeting, the Specialist will convey one of the following four decisions of the board in writing to the investigator:

- **Approved as submitted:** If a study is **approved as submitted** (no stipulations required by the board), a letter of approval is sent through the online system to the principal investigator stating the date of approval and duration of approval. The approved consent document and recruitment materials (if any) are watermarked with the date of RSRB approval expiration and available for downloading from the [RSRB online submission system](#) (ROSS).

The investigator is responsible for providing notification of RSRB approval to funding agencies or other entities.

- **Approved with stipulations:** If a study approval is **pending approval of minor revisions** (changes that do not affect subject safety), the Specialist will send a letter to the principal investigator to request these changes. **Subjects may not be enrolled to the study until the requested revisions are made and notice of approval is received.** The RSRB Chair may approve the study upon receipt of the revisions without further action by the full board. After the RSRB Chair approval, an approval letter is sent through the online system to the principal investigator stating the date of approval and duration of approval. The approved consent document and recruitment materials (if any) are watermarked with the date of RSRB approval expiration and available for downloading from the [RSRB online submission system](#) (ROSS).
- **Tabled:** This means that substantive issues regarding the protocol and/or consent form(s) must be addressed before the board can determine the acceptability of the research. Clarifications or requested revisions may have a significant impact on subject safety or understanding. A notification is sent through the online system to the investigator requesting that these issues be addressed. Subsequent convened meeting review of the investigator’s response is required prior to approval.
- **Disapproved:** This means that unresolved questions regarding the rights and welfare of the subjects are of such significance that the RSRB determines approval of the study to be unwarranted. A notification is sent through the online system to the investigator, which explains the reasons for the disapproval.

Principal Investigators may appeal a disapproval decision made by the RSRB. Such appeals will be heard (either in person or in writing) by the RSRB. Upon consideration of the appeal materials and/or presentation, the decision may stand (disapproval) or, if appropriate, the decision may be to approve as resubmitted, or approve after additional modifications. As disapproval of studies may only be an action of the convened RSRB,

approval of a previously disapproved study may only be given at a convened meeting of the RSRB.

Responsibilities of the Principal Investigator for Research in Progress

The approval letter states the responsibilities the investigator has to the RSRB while the research is being conducted. These responsibilities include:

- Conducting the research only in accordance with the protocol/study design (e.g., following inclusion/exclusion criteria) as submitted and approved by the RSRB, and requesting approval of any proposed changes in the research activity.
- Reporting any unanticipated problems involving risks to subjects or others.
- Applying for study re-review and providing reports on the progress of the study in a timely fashion.
- Using only consent forms bearing a current “RSRB Approved” watermark.
- Obtaining approval of all recruitment materials/methods before use.
- Maintaining all approved study documents in a study file.

Proposed Changes / Amendments

Any changes to the protocol, consent form or research process must have RSRB approval. These revisions may be as minor as an updated investigator telephone number or as major as the addition of a new experimental arm. Whatever the nature of the change, RSRB review and approval is required before the change may be implemented. The only exception to this prior approval requirement is when a change is necessary to protect subjects from an immediate hazard, in which case, a report of the change and a formal request to amend the study are to be made promptly to the RSRB. The request for amendment may be submitted by the principal investigator or by an individual authorized by the PI.

Remember that, in addition to submitting revised study materials, appropriate changes must also be made to the original online application.

Amendments involving greater than minimal risk will be reviewed at a convened meeting of the board. Amendments involving minor changes will be given expedited review. Minor changes eligible for expedited review are those that do not change the risk/benefit ratio of the study; do not increase the risk presented by the study above minimal risk or, in and of themselves, do not expose more people to the risk, and do not present more than minimal risk.

Examples of amendments requiring convened meeting review:

- Expansion of the eligibility criteria to a study involving greater than minimal risk (e.g., revising the inclusion criteria to permit the enrollment of individuals with more serious illness)
- Increasing the overall accrual goal to a study involving greater than minimal risk
- Discovery of additional toxicities prompting a revision to the consent form

Examples of amendments qualifying for expedited review:

- Increase in accrual goal to studies involving minimal risk
- Administrative or editorial revisions, regardless of study risk (e.g., change in investigator address or correction of typographical errors)
- The addition of subject recruitment materials (e.g., advertisements)

After approval, an approval letter and revised versions of the watermarked or stamped consent and recruitment materials (if applicable) will be available to the principal investigator for downloading from the [RSRB online submission system](#). The change may be implemented as soon as this approval is given/received.

When amendments impact the safety of subjects previously enrolled and continuing on study intervention, it may be necessary to convey this information (i.e., to obtain the continued consent of the subjects) by means of an addendum to the existing consent form or by using a new form. The RSRB may determine, for example, that subjects must be notified of new findings or toxicities not noted at the time they were originally enrolled. Such notification is consistent with the view that informed consent is a continuous process, and affords subjects the opportunity to determine whether or not they wish to continue their participation in the research. The RSRB will determine on a case-by-case basis when such notification, and its documentation, is required.

NOTE: Approval of amendments **does not** extend the original project approval period.

Reporting unanticipated problems -- adverse experiences and deaths

Principal investigators are responsible for reporting to the RSRB unanticipated problems that impact the safety of or risk to their subjects or others. These are reported using the “New Reportable Event” tab in the [RSRB online submission system](#).

The following definitions apply:

- **Serious adverse drug experience:** Any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- **Unanticipated adverse device effect:** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, the frequency, specificity or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated

serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

- **Unanticipated problem involving risk to subjects or others:** Any problem or event that was not expected given the nature of the research, the population under study and the procedures in the study, and which affects the rights, safety, or welfare of subjects or others (e.g., those not directly involved in the research such as research staff or family members), and is related to the research intervention, research procedures, and/or conduct of the research study. The effect may be an actual harm or discomfort that is caused, or it may cause an increase in risk.
- **Unexpected adverse drug experience:** Any adverse drug experience (associated with the use of the drug), the frequency, specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to subjects and the RSRB.
- **Unexpected versus Unanticipated:** “Unexpected” implies an experience where the frequency, specificity or severity is not consistent with the current risk information provided to subjects and the RSRB. “Unanticipated” implies an experience that was not expected given the nature of the research, the population under study and the approved procedures or protocol for conduct of the study. Therefore, one type of adverse event may be the theoretically possible, but not expected (e.g., anaphylaxis, which would be unexpected), while another might not be considered possible, so its occurrence would be truly unanticipated.

Investigators are required to report any of the following occurrences:

1. Unanticipated problems involving risks to subjects or others, which occur in a UR study or that affect UR subjects or the conduct of the UR study

An unanticipated problem involving risks to subjects or others may include any event that was not expected given the nature of the research, the population under study and the approved procedures or protocol for conduct of the study. These problems involve risk to subjects or others (for example, research staff, family members, or others not directly involved in the research), and are related to the research intervention, research procedures, and/or conduct of the research study. The risks (including physical, financial, legal, social, emotional, psychological well being, subject privacy, or data confidentiality) may affect the rights, safety, or welfare of subjects or others. When a research study includes investigational drugs or devices, some unanticipated problems may also meet the definition of an unexpected adverse drug experience (serious or otherwise), or an unanticipated adverse device effect.

Investigators must report any such unanticipated problems involving risk to subjects or others, regardless of whether they occur during the study or after the study (i.e., some unanticipated problems may only be discovered in the analysis phase). This report should include a description of the event, the date of occurrence, whether it is a UR or non-UR event, the type of risk, and its effect on subjects and/or others. Reports must be submitted within 15 calendar days of the event or notification to the investigator of the event, whichever is earlier, unless they are life-threatening or they resulted in death, in which case notification of the event must be given immediately (telephone, facsimile, e-mail, or in person). This immediate notification must be followed by a written report filed within seven calendar days.

Unanticipated problems may include any of the following:

- Information that indicates a change to the risks or potential benefits of the research

- A breach of privacy or confidentiality
- Change in labeling or withdrawal from marketing of a drug, device or biologic used in a research protocol
- Incarceration of a subject in a protocol not approved to enroll prisoners
- Complaint of a subject that indicates unexpected risks or that cannot be resolved by the research team

Among the actions that the RSRB may consider:

- No action
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to past subjects
- Notification of current subjects when such information may relate to subjects' willingness to continue to take part in the research
- Requirement that current subjects re-consent to participation
- Modification of the continuing review schedule
- Monitoring of the research
- Monitoring of the consent process
- Suspension of the research approval
- Termination of the research approval
- Referral to other organizational entities (e.g., OHSP, University Audit, UR Office of Counsel)

2. Unexpected, related adverse drug/biologic event

For subjects enrolled by UR investigators, the investigator must report to the RSRB any unexpected adverse drug events. By definition, these events must be associated with the use of the drug/biologic. Investigators may become aware of unexpected adverse drug events, not occurring at UR, which involve risks to subjects or others previously unknown and that the investigator believes require a modification to the UR study. This type of external event must also be reported.

Investigators must report a description of the event, the date of occurrence, the type of harm or risk, whether the event was unexpected, the outcome, and an assessment of degree of relatedness to the research. The report also must include the proposed actions to be taken by the investigator including change in consent documents or other notification procedures and notifying current subjects.

Adverse events that are serious and unexpected and related to the research (possibly or probably) must be reported to the RSRB within 15 calendar days.

- "Serious" is any event in which the outcome results in any of the following: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Events that may not result in death, be life-threatening, or require hospitalization are considered serious when medical or surgical intervention is required to prevent one of these outcomes.
- "Related" is the degree of causal association that can be attributed to the study/agent.
- "Unexpected" means the event was not previously identified in nature, severity, or degree of incidence in the investigational plan or [RSRB online application](#), or an adverse experience that has not been previously observed.

Reports must be submitted within 15 calendar days of the event or notification to the investigator of the event, whichever is earlier, unless they are life-threatening or they resulted

in death, in which case notification of the event must be given immediately (telephone, facsimile, e-mail, or in person). This immediate notification must be followed by a written report filed within seven calendar days. For adverse events that are not serious and unexpected and related, a summary report should be submitted to the RSRB at the time of the study's continuing review.

Reports of serious and unexpected adverse drug events occurring in a UR subject are reviewed by an RSRB Chair to verify that the event would be considered "unexpected" based on the information previously reviewed and approved by the RSRB and to determine if the event involved risks to subjects or others. If the Chair verifies that this information is correct, the report is scheduled for review at the next available convened meeting. At a convened meeting, the board determines whether current/former subjects must be notified of the new information, and if so, the method of notification and whether any study materials (e.g. consents, protocol) must be updated to reflect the new information. The range of possible actions that the RSRB may consider includes those outlined in 1 above.

Based on the frequency and seriousness of adverse events, the RSRB may deem it necessary to suspend or terminate a research study or studies. The RSRB will involve the investigator in making such a decision.

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

3. Unexpected, related adverse device effect

Procedures for devices are the same as for drugs and biologicals in 2 above.

4. Receipt of new information (including risks or benefits) that may impact the willingness of subjects to participate or continue participation in the research study

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

Investigators must report any new information that may impact the willingness of subjects to participate including a description of the new information and its potential affect on subjects (prospective, current and former) and the investigator's proposed method for providing this information to subjects. Reports must be submitted within 15 calendar days of the event or after the investigator becomes aware of the event/ information, whichever is earlier.

Reports and modifications related to new information are reviewed by an RSRB Chair to determine if a notice to subjects is warranted and if the method and information provided to subjects is appropriate. If the Chair verifies that this information is correct and notification is appropriate, the Chair approves the report and modification. The Chair may refer the review to the convened meeting when it is believed the information or notification method is not appropriate, or if the new information significantly affects the safety of current, former or potential subjects. When protocol changes are immediately required to eliminate apparent

immediate hazards to subjects, the Chair may approve subject notifications prior to convened meeting review.

5. Noncompliance with federal regulations or the requirements or determinations of the IRB

Investigators should self-report non-compliance with federal regulations or the requirements or determinations of the RSRB and include a description of the occurrence, as well as any effect on the rights, safety, or welfare of subjects or others. These reports are reviewed by the RSRB specialist and chair. Whether the Chair confirms the information and determines that notification is appropriate, or if there are additional issues that need to be resolved, the occurrence is presented as a report to the next available meeting of the full board. The range of possible actions that could be taken by the RSRB includes those outlined in number 1 above. When protocol changes are immediately required to eliminate apparent immediate hazards to subjects, the Chair may approve notifications prior to convened meeting review. Any serious or continuing noncompliance is reported to oversight authorities as described in section on Addressing Allegations of Non-compliance below.

6. Changes made to the research without prior RSRB approval to eliminate apparent immediate harm

Investigators must report any changes made to research without prior RSRB approval to eliminate apparent immediate harm. This report should include a description of the event, the date of occurrence, whether it is a UR or non-UR event, the type of risk, and its effect on subjects and/or others. Reports must be submitted within 15 calendar days of the event or notification to the investigator of the event, whichever is earlier, unless they are life-threatening or they resulted in death, in which case notification of the event must be given immediately (telephone, fax, email or in person). This immediate notification must be followed by a written report filed within 7 calendar days.

The range of possible actions that could be taken by the RSRB includes those outlined in number 1 above.

7. Reports from a: Data and Safety Monitoring Board, Data Monitoring Committee, Independent Safety Monitor, Study Coordination Center, Study Group Center

Monitoring reports indicating an increased risk to subjects (usually reflected as a proposed revision to the consent form and/or protocol) are to be submitted to the RSRB within 15 calendar days after the investigator receives them. All other monitoring reports (e.g. those allowing the study to continue unchanged) are to be submitted with the progress report at the time of continuing review.

The range of possible actions that could be taken by the RSRB includes those outlined in number 1 above.

8. Investigator-initiated voluntary suspension of research

Investigators may suspend all or part of a research study (enrollment, test procedures, etc) to consider changes to the research, investigate risks to subjects or others, etc. These reports keep the RSRB apprised of the status of approved research.

Reporting by the RSRB to funding and regulatory authorities

When unanticipated problems involving risks to subjects or others are reported to and substantiated by the RSRB, the Executive Director will prepare a report, with appropriate

consultation, and send it to OHRP (in accordance with the terms of the UR Federalwide assurance), the FDA (for projects subject to FDA regulations), and to other federal agencies when they have auspices over the research and require reporting separate from that to OHRP. Copies of the report are sent to the investigator and the investigator's department Chair, the RSRB and its Chair, the Director of OHSP, WIRB (as appropriate) and UR legal counsel. Under normal circumstances, this report will be sent within 60 days of the final RSRB determination/action.

When a problem occurs in a study reviewed and approved by WIRB, the investigation may be conducted by WIRB or by the RSRB (if requested to do so by WIRB), but in all cases, the external reporting will be conducted by the RSRB Executive Director.

Continuing Review

When a study is first approved by the RSRB, the duration of approval is noted. By federal regulation, approval can be given for a period of no more than one year (365 days). Examples of factors in addition to risks and potential benefits that the RSRB may consider in determining the duration of approval include:

- prior RSRB interaction with the investigator
- the experience of the investigator
- the types/condition of subjects
- prior unanticipated event reports
- stage of study and subject disease states

The RSRB also requires continuing review of studies closed to new enrollment but on which subjects are still receiving interventions or remain in long-term follow-up.

NOTE: The RSRB cannot extend a study approval period without conducting review of the progress report and related materials. "Grace periods" or "administrative extensions" are not allowed by federal regulation.

The continuing review procedure begins with submission of a **Continuing Review Form**. The report form is available online and a notice of due date will automatically be sent to the investigator's email inbox. The investigator will be prompted to login to the online study file and submit an online **Continuing Review Form**.

If the report is not received after the first notice, the RSRB will send a reminder at 60 days before study expiration. If, 30 days after the second notice, a progress report still has not been received, a third reminder ("pending suspension notice") will be forwarded to the investigator.

If no continuing review report is returned by the expiration date, a notice of study expiration will be sent, which will also indicate that study closure/termination is pending. **Research activities must stop upon expiration (including recruitment enrollment, interventions, interactions and data analysis on current subjects)**. Note: Investigators may request the continued participation of subjects enrolled to expired studies, if there is an overriding safety concern or ethical issue that would make such continuing participation in the subject's best interest.

Termination letters are issued after the study has been expired for over 30 days and are copied to the PI's department chair. **Investigators whose studies are suspended/terminated due to failure to submit a progress report will not have new studies reviewed by the RSRB until a progress report is submitted and the Continuing Review is completed or the study is formally closed.**

It is the investigator's responsibility to complete the continuing review report, including any documents specified in the form, and to submit the report at least 8 weeks (60 days) prior to the date of RSRB approval expiration.

The RSRB applies the same standards and procedures used for initial approvals to the continuing review process (i.e., convened meeting of the full board or expedited review). Studies initially granted convened meeting approval may be given expedited continuing review if no subjects have been enrolled and no additional risk to the study has been identified.

Notes regarding continuing review:

- The RSRB is required to conduct continuing *review* at least annually. The RSRB may require stipulations for continuing approval. To ensure uninterrupted protocol activity, these stipulations – some of which may require review at a convened meeting – must be met before the RSRB approval expiration date.
- By federal guidelines, the RSRB can conduct continuing review *no sooner than 30 days* prior to a study's expiration date. The RSRB notifies investigators to submit continuing review reports 3 months in advance of this date to allow investigators ample time to file the report and resolve any issues that may have an impact on the continuing approval.

Reapproval of Consent and Recruitment Documents

Studies that continue to accrue subjects (or continue to collect subject specimens or data) are required to use the most recently approved consent documents or recruitment materials. Upon reapproval, the documents will be given an updated approval stamp/watermark with the new expiration dates. The continuing review form prompts the investigator to identify any consent/recruitment documents that do not require reapproval (i.e. study closed to enrollment).

As a condition for reapproval, the investigator must submit a copy of the consent form signed by the last subject enrolled to the study. If the study involves the enrollment of more than one subject population (e.g., adults and children or patients and healthy volunteers), submit a signed consent form representing *each* population. If there are two versions of the consent form, e.g., Spanish and English, and both have been used to enroll subjects, then the last signed consent form for each version must be sent.

5-Year Continuing Reviews

To ensure appropriate review of current information in long-term studies, the RSRB requires that every five years the principal investigator submit an updated protocol with all prior amendments included in addition to the completed continuing review report.

NOTE: The following exceptions are made to the 5-year continuing review request:

- Clinical research trials closed to enrollment, for which all interventions are complete, and in which subjects remain solely in follow-up.
- "Umbrella studies," i.e., projects that serve as funding vehicles for other studies, which are reviewed as separate research activities. (Note: studies that were not originally submitted in the online system must be submitted online at the first 5-year review.)

Study Completion or Closure

The RSRB requires submission of a final report for completed studies. Submit the Continuing Review Report to notify the RSRB of the closure or completion of a research study, whether at the time of continuing review or at any time during the approval period when the study closes. A request to close studies that have not been initiated (no enrollment) is also required. Upon receipt of a completed form, the RSRB office will permanently close the file. As appropriate (i.e., human subject protection issues involved), closure reports will be referred to the RSRB Chair for review.

NOTE: Remember to include the date of study completion when submitting the final closure report. The date of completion is when all subjects have completed all interventions and the investigator has completed the analysis as described in the study plan/protocol.

Non-Compliance

The University recognizes the implicit and paramount importance of compliance with laws, regulations and policies when conducting human subject research. As such, the reporting of *possible* non-compliance is the responsibility not only of the research team but of any individual who suspects its occurrence.

Definitions and Reporting of Non-Compliance

- **Non-compliance:** Failure to follow the federal regulations or state laws for the protection of human subjects in research or failure to follow the requirements or determinations of the RSRB with respect to the conduct of research as approved by the RSRB.
- **Serious non-compliance:** Non-compliance that results in an increased risk to subjects or others. Non-compliance may also be deemed serious when it involves fraud and/or scientific misconduct, even in research posing minimal risk to subjects.
- **Minor non-compliance:** Non-compliance that does not result in an increased risk to subjects or others. Minor non-compliance, for example, may involve records or procedures that, while not correct, do not adversely affect the validity of consent or the safety of subjects.
- **Continuing non-compliance:** A pattern of non-compliance that continues despite identification by the RSRB, notice to the investigator, or prior submission of a corrective action plan. This pattern may or may not result in increased risk to subjects.
- **Sporadic non-compliance:** Non-compliance that does not indicate a pattern and does not result in increased risk to subjects.
- **Allegation of non-compliance:** An unproven assertion of non-compliance.

Allegations of Non-Compliance

An Allegation of non-compliance may be initiated in a number of ways, for example:

- **Continuing review** - The RSRB may learn of potential non-compliance through its continuing review of ongoing research.
- **Direct report by an individual/organization to the RSRB** - An allegation of non-compliance may be reported directly to the RSRB Office by any individual, including a subject, subject's family member or representative, a UR employee (who may or may not be associated with the research team), etc. Allegations may also come from regulatory agencies and sponsors.
- **Audit by the UR Office of Human Subject Protections (OHSP)** - As part of its activities, the OHSP conducts routine and for-cause audits of research studies approved by the RSRB. These audit reports may reveal area(s) of non-compliance.
- **Medical Center Office of Compliance** – The Office may forward complaints to the RSRB it received from employees or from calls to the compliance hotline.

Addressing Allegations of Non-Compliance

Each allegation of non-compliance will be evaluated to determine whether it is valid or has no basis in fact. A collaborative approach is applied when an evaluation of an allegation of non-compliance is required.

The RSRB specialist, chair and executive director will review the allegation to ensure that information about the allegation is as complete as possible and determine what, if any, additional details are needed. Depending upon the nature of the situation, and in keeping with the collaborative evaluation, further investigation may be made by one or more OHSP/RSRB office staff and/or a team consisting of RSRB office staff, board members, OHSP staff and other University personnel (legal counsel, for example). The following steps may be taken: Following the conclusion of this inquiry phase, the chair may take the following action:

- a) Determine the allegation has no basis in fact and close the investigation
- b) Administratively develop a corrective action plan to be reviewed by the board (for cases in which the non-compliance is neither continuing nor serious)
- c) Refer the case to the convened board to determine whether the allegation is valid and whether the possible non-compliance is continuing or serious

Findings of Non-Compliance

It is not the intent, nor the scope, of the RSRB to punish investigators; however, noncompliance does have consequences for the research/investigator, e.g., if legally effective informed consent is not obtained when it should have been, it is a logical consequence that any/all data collected from those non-consented or improperly consented subjects may not be used for research purposes. Noncompliance that raises academic discipline issues (e.g., scientific misconduct) will be referred to the proper University channels for action. The focus of the remedies required by the RSRB is always the safety and welfare of subjects.

A finding of non-compliance means non-compliance supported by facts. All findings of serious or continuing non-compliance are made by the convened RSRB. Actions of the convened board are based on the nature and severity of the non-compliance. Among the actions the convened board may consider:

- Dismissal of the allegation (if not valid)

- No action (e.g., for minor, sporadic incidents, closed studies, etc.)
- Cautionary reminder
- Modification of the protocol (i.e., amending the previously approved protocol)
- Modification of the information disclosed during the consent process
- Providing additional information to former subjects
- Notification of current subjects (when such information may relate to their willingness to continue to take part in the research)
- Requiring subjects to renew consent to participation or to *post hoc* data use
- Modification of the continuing review schedule
- Monitoring of the research
- Monitoring of the consent
- Remedial education of the investigator
- Restriction of data use/publication
- Restriction of investigator's research approvals
- Suspend or terminate approval (definitions below)
- Referrals to other University of Rochester Departments (i.e. OHSP, University Audit, Office of Counsel)

Suspension - temporary cessation of RSRB approval of some (e.g., no new enrollment) or all activities in a currently approved research study.

Termination - permanent withdrawal of RSRB approval (i.e., closure of the research study). The same procedures and considerations apply as for study suspension.

When study approval is suspended or terminated for serious or continuing non-compliance, the convened board will:

- Consider what actions are needed to protect the rights and welfare of currently enrolled subjects (e.g., making arrangements for medical care, continue the research with a transfer to another investigator – with or without independent monitoring)
- Consider whether procedures for withdrawal of enrolled subjects protect their rights and welfare
- Determine whether subjects must be informed of the suspension or termination
- Require any unanticipated problems, adverse events or outcomes to be reported to the RSRB

During the period of suspension or termination, all research activities must stop, including recruitment, enrollment, interventions, interactions, and data analysis on current subjects, unless the RSRB finds that there is an over-riding safety concern or ethical issue that would make continuing participation in the best interest of the subject(s). The board may consider withholding consideration of new proposals until the suspension ends or the termination reason is adequately addressed.

Note: The RSRB is obligated to report suspensions, terminations and serious/continuing noncompliance to other organizational entities (e.g. OHSP, University Audit, UR Office of Counsel) and federal agencies (e.g., NIH, NSF, OHRP and FDA, as appropriate).

Recruitment and Consent Guidelines

NOTE: For a helpful discussion on obtaining and documenting consent, click here: <http://www.rochester.edu/rsrb/documents/pdf/consentguidance.pdf>

Recruitment of Human Research Subjects through Advertising

Direct advertising for study subjects (i.e., advertising that is intended to be seen or heard by prospective subjects) is considered part of the informed consent and subject selection processes. The aim of RSRB review is to ensure that the information is not misleading to subjects. This is especially important when a study may involve subjects who are likely to be vulnerable to undue influence, for example, financially constrained subjects.

- **Included** are: websites, newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects.
- **Not included** are: communications intended to be seen or heard only by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), news stories, and publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

When direct advertising to potential subjects is to be used, the RSRB must review both the information contained in the advertisement and the mode of its communication. This is to confirm that the procedure for recruiting subjects is not coercive and that the recruitment material does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.

The RSRB reviews the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the RSRB reviews the final audio/video tape. The PI should request a review and approval of the wording of the advertisement (i.e., the script) prior to taping to avoid re-taping because of inappropriate wording. In that case, the review of the final taped message prepared from RSRB-approved text may be accomplished through expedited procedures.

Recruitment press releases (those that provide a contact name or number) require review by the RSRB. This review is conducted on an expedited basis.

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment" or "new medication." A phrase such as "you will receive new treatments" incorrectly implies that all study subjects will receive products of proven worth newly approved by the FDA. Advertisements should not promise "free medical treatment" when the intent is only to say subjects will not be charged for taking part in the investigation.

If an investigator decides that advertising for subjects is needed after the study has received RSRB approval, the request and advertising materials may be considered a minimal risk amendment, which qualifies for expedited review.

Generally, advertisements should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements:

- The name and address of the investigator and/or research facility (e.g., University of Rochester) and the person or office to contact for further information
- The purpose of the research (e.g., the condition under study or goal of the project)
- The general criteria, in summary form, that will be used to determine eligibility for the study (e.g., healthy adults between the ages of x and y)
- The time or other commitment required of the subjects
- A brief list of participation benefits, if any (e.g., a no-cost health assessment). Note: payments to subjects for participation are not benefits; they are inducements.

Advertisements may state that subjects will be paid, but they should not emphasize the payment or the amount to be paid.

Advertising over the Internet

According to the FDA, RSRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.

Examples of clinical trial listing services that do not require prospective RSRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ), the NIH/CTSA ResearchMatch and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, RSRB review and approval is required to assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

Recruiter/Receptionist Scripts

The first contact prospective study subjects make is often with a recruiter/receptionist who follows a script to determine basic eligibility for the specific study. The investigator should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. In some cases personal and sensitive information is gathered about the individual. The RSRB should have assurance that the information will be appropriately handled. A simple statement such as "confidentiality will be maintained" does not adequately inform the RSRB of the procedures that will be used.

Examples of issues that are appropriate for RSRB review: What happens to personal information if the caller ends the interview or simply hangs up? Are the data gathered by a marketing company? If so, are names, etc. sold to others? Are names of non-eligible subjects maintained in case they would qualify for another study? Are paper copies of records shredded or are readable copies put out as trash? The acceptability of the procedures would depend on the sensitivity of the data gathered, including; personal, medical and financial.

When principal investigators wish to recruit subjects from populations to which they do not have routine access (e.g., the patients of other physicians or institutions) to a research study, they may not contact these patients directly (i.e., no "cold calls"). The following procedure is to be used:

- The PI provides a written description of the project to the person having access and a relationship (e.g., the treating physician) with potential subjects, explaining that he/she would like to recruit subjects for research.
- The person with access makes the project description available so that the potential subjects have the opportunity to consider whether or not they may wish to get more information about participation.
- Potential subjects can choose to contact the PI either by phone or in writing (e.g., return mail) to gain further information and continue to consider the project.

Informed Consent

Informed consent is a basic ethical obligation for researchers and enforced by federal regulation. Informed consent is not just a form. It is a process of information exchange that takes place between the prospective/enrolled subject and the investigator, before, during and sometimes after the experiment. The informed consent process is not a single event, but continues as the study progresses. Subjects should feel free to ask questions at any time. The amount of information

that needs to be presented both in writing (i.e., the consent document and related materials) and orally is directly related to the risk that the study presents and the complexity of the research procedures.

The manner and context in which information is conveyed is as important as the information itself. There must be no coercion or undue influence. Subjects must have sufficient time to decide and should be allowed to consult with family and/or others if needed.

Subjects are considered to be “enrolled” in a study once they have given consent (written or, if approved, orally). No study-related procedures are allowed until legally effective informed consent has been obtained. In studies where a screening/selection process is needed, it may be necessary to obtain consent for the screening in addition to or combined with the study consent. (Note: the protocol should describe how subjects are identified and enrolled as well as how persons who are screened, enrolled, withdrawn and “lost to follow-up” will be reported to the RSRB and, if applicable, to the sponsor.)

The purpose of a consent form is to provide a written source of information and a place to document that a subject’s consent has been given before the start of the study. Consent forms must be signed and dated by the subject (or the subject’s authorized representative) before any research procedures may begin. The form is important because it serves as a baseline of information for initial presentation, a reference source during the study, and documentation of voluntary participation. The complete original signed consent form is retained in the investigator’s study records and a copy is given to the subject.

Remember that the study plan/protocol needs to address the consent process. It should describe who will obtain consent and how the process of informed consent will promote thoughtful decision-making by subjects. Steps taken to determine comprehension and to minimize undue influence should be explained, especially when the study will include vulnerable populations such as children and the terminally ill. If all subjects will not be capable of providing consent, the study plan/protocol needs to describe the process used to obtain permission of authorized representatives. If an auditor-witness and/or translator is used, their function should be explained. The protocol should also explain how consent will be documented and how the forms will be stored.

NOTE: Only the approved investigators, co-investigators and sub-investigators may obtain consent, unless the protocol/study plan specifically details others. Everyone obtaining consent at UR must be trained through the HSPP/EPRP program.

Clinical investigators may wish to place research consent forms in the medical record to inform/alert health care providers. For consent documents that are to be retained in the subject’s medical record, use the Strong Memorial/Highland Hospital form number SMH-101 or HH-101, respectively, in the upper right-hand corner and provide space either for addressograph or hand entry of the subject’s name and chart number. (Note: the original signed consent form should be kept by the investigator in the study records; only copies should be placed in the medical record.)

Consent form templates are included on the RSRB website:

<http://www.rochester.edu/rsrb/submission-documents/index.html>

The CRC has guidelines regarding specific consent form wording for procedures conducted on its facility. Click here to access these guidelines:

<http://urmc.rochester.edu/ctsi/research/crc/documents/SuggestedWordingforCRCProceduresforProtocols-Consents.doc>

When preparing the consent form, keep the following points in mind:

- Consent forms must be understandable to the subject population. In other words, avoid lengthy sentences and technical terms like this:
 - *Subjects suffering from this condition may indirectly benefit from the research through the further understanding of the mechanism of pain (central vs. peripheral) accrued from the findings.*...and instead say this:
 - *You may or may not benefit by taking part in this study*

Remember: The term “understandable” pertains to the language commonly spoken by the subject population. Investigators who anticipate enrolling even one subject who only speaks a language other than English need to translate the entire consent form into that language. This translation may be done after an English form has been approved, but translated forms must be approved by the RSRB before use.

- Information in the consent form must agree with the study plan/protocol and the [RSRB online submission system](#). It’s not uncommon for protocols to go through a number of revisions before and after they’re submitted to the RSRB. Some of these revisions may be to protocol elements that are repeated/reflected in the consent form (e.g., the number/kind of tests). Make sure the protocol, application and consent are consistent (e.g., not 3 tests in the consent and 4 in the protocol).
 - Aim for an eighth-grade reading level (most word processors can generate reading level scores).
 - Write as if you were talking to the subject (in 1st person) – in a conversational tone – not about the subject (in 3rd person). Use active rather than passive voice. For example, rather than say:
 - A pregnancy test will be administered to you./The subject will be given......say:
 - You will have a pregnancy test.
 - Do not use, “I understand that...” This terminology is coercive, implying a level of understanding the subject may not have.
 - The project title in the consent form may be the actual title on the review application and grant/contract, or, if it helps the subject understand the study, it may be simplified (as long as it isn’t incorrect or misleading).
 - Use subheadings and white space to improve readability in long forms.
 - Replace scientific, medical and technical terms with lay terms.
- Click here for a glossary of frequently used terms:*
<http://www.rochester.edu/rsrb/documents/pdf/layterms.pdf>
- Use lists, tables and charts to show complex schedules and study designs.

- Use type no smaller than Times New Roman 12 point. Consent forms for elderly subjects and those with visual impairments may benefit from even larger type.
- Use departmental letterhead for the first page.
- Include a footer that numbers the pages (e.g., 1 of 6, 2 of 6, 3 of 6...), shows the version date and the RSRB study number.

Elements of consent

Although each research study involving human subjects is unique, the federal regulations and the RSRB require that all consent forms contain the following information elements:

- An introduction, including a statement that the study involves research
- An explanation of the purpose(s) of the research
- Description of study procedures (identifying both standard of care procedures and any that are experimental)
- Expected duration of subject involvement
- A description of any reasonably foreseeable risks or discomforts of participation
- Benefits of participation to the subject or others
- Appropriate alternatives or course of treatment that might be advantageous to the subject (not applicable if the only alternative is non-participation)
- UR standard wording for compensation for injury (for studies involving greater than minimal risk)
- Confidentiality of Records statement (and, if applicable, HIPAA authorization)
- Contact persons (for questions about the research, research-related injury and subject rights)
- Statement that participation is voluntary
- Statement that subjects will receive a signed copy of the consent

Federal regulations and the RSRB require several other elements of information if they apply to the study and are important for subject to know. These additional elements often apply to FDA-regulated studies. Additional elements include:

- A statement that the particular treatment or procedure may involve risks to the subject that are currently unforeseeable
 - Include for research involving investigational or marketed drugs or devices for which toxicities are not well-studied in humans.
- A statement that, if the participant is or becomes pregnant, the particular treatment or procedure might involve risks to the embryo or fetus, which are currently unforeseeable
 - Include for research involving investigational or marketed drugs or devices for which effects to a fetus are unknown in subjects who are or might become pregnant.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's wishes (e.g., side effects of a study drug are too severe or the sponsor terminates the study)
- Payments (incentives and/or expense reimbursements if any)
- Additional costs to participate (e.g., hospitalization, cost of testing or transportation to and from the research site)
- Consequences of withdrawal (adverse health/welfare effects, if any) and procedures for withdrawal that protect the subject's safety

- Include if any adverse health or welfare effects may be anticipated (e.g., the need to taper a drug treatment), or whether additional tests may be needed to help ensure the safety of the subject after withdrawal.
- Remember that the consequences of withdrawal are not intended to coerce the subject into continuing to take part.
- Statement that subjects will be informed of new findings that may relate to their willingness to take part (findings of a data & safety monitoring board raise safety concerns, for example, or new toxicities that develop)
- Number of subjects (if this poses a risk to privacy, for example, or to provide the subject the risk exposure/context in which the study takes place)
- Probability of random assignment to placebo or experimental arm (e.g., one in two, like flipping a coin; or, one in four like drawing numbers from a hat)
- Funding statement for sponsored studies
- Conflict of interest statement(s) if applicable (both investigator and University)

Consent issues in research involving children (subjects under 18 years of age)

In all research involving human subjects, the agreement to participate is an essential protection of their rights and welfare. Children, by definition, cannot give legal consent. Therefore, a combination of assent (agreement) of the child subject and permission of the parent or legal guardian is generally deemed an adequate substitute. If either the parent refuses permission or the child subject refuses assent, the child should not be enrolled.

The University of Rochester requires the permission of parents for research that involves children. There are four exceptions to this general policy which may be requested by investigators:

- 1) no-risk or minimal-risk research with older adolescents (e.g., anonymous surveys in high school students)
- 2) purely observational studies (no intervention) of public behavior (e.g., classroom activities)
- 3) studies of existing data and
- 4) research with children in those circumstances where New York Law expressly gives children the right to seek certain types of medical treatment without parental consent.

NOTE: Except for studies involving existing data, research involving children for which waiver of parental permission is requested must be reviewed and approved by the Senior Associate Dean for Clinical Research, as a condition for RSRB approval.

Adequate provision must be made for soliciting the assent of those children capable of providing a meaningful agreement. The process must be appropriate to the study as well as to the age, maturity and psychological state of the child. Information must be presented in language and format that is understandable to the child. The children should have an understanding of the research procedures and it should be clear that their participation is voluntary. In long-term studies where subjects are enrolled as children, but who will reach their 18th birthday, provisions must be made for obtaining their consent as adults.

An exception to the assent mechanism is made for children with life-threatening illnesses who are entered into open-label treatment protocols with the expectation of benefit. In these cases the permission of the parent is sufficient, but the understanding of the child subjects is still desirable. Assent in the sense of agreement is not sought from the child subject because if he/she does not agree, the parent's wishes will prevail. It would be disingenuous to ask for agreement when negative responses will be ignored. The non-agreement of the child, especially in older children

(e.g., 17) may be ethically troublesome. The University medical center offers a Clinical Ethics Consultation Service that may be helpful to subjects, families and staff.

It is important to note that the permission of caregivers and/or service providers is not sufficient to conduct research with children. Only parents and legal guardians have that authority and responsibility. School principals, teachers, clinic personnel, etc., do not have the authority to give blanket' permission for their students/patients/clients to participate in research. In classroom research, it must be made clear that the research is not part of the regular educational program and that the student's grades or standing will not be affected by not participating.

Incentives for participation must be appropriate to the ages of the subjects and the nature of the study. Incentives (e.g., toys, coupons for food) should usually be given to the child subjects, not the parents. Parents may be reimbursed for out-of-pocket expenses such as travel.

Documentation of the child-subject's assent and the parents' permission depends upon the nature of the research. Usually, adolescents (teenagers) can sign 'assent' forms, but for younger children an assent script may be used to document presentation of the information and the subject's verbal agreement. In most other cases, documentation of parental permission should be on a signed permission form that follows the guidelines for consent forms. Some research with children may require the permission of both parents, in which case a signature line for each must be provided on the consent form.

NOTE: One of the main goals of assent in studies for which participation is optional is to let children know that they are not required to take part in the research, even if their parents say it is okay.

For consent/permission/assent guidelines, see [Appendix 2](#).

Consent Issues in Adult Subjects with Decisional Impairment

The University has developed a policy delineating the consent process for adult subjects with decisional incapacity. See Appendix 1.

Under this policy, the RSRB accepts consent to research given by an authorized representative for:

- 1) research that poses no greater than minimal risk (whether or not there is a possibility of benefit);
- 2) research that poses minimal risk or greater than minimal risk, but offers a possibility of direct benefit, or
- 3) research involving slightly greater than minimal risk and offers a possibility of benefit to the class of subjects. (Note: this category requires additional approval by the Senior Associate Dean for Clinical Research and notification to URM legal office).

Telephone consent by an authorized representative - While the FDA allows investigators to obtain consent by telephone from a legally authorized representative, such practice presents ethical difficulties. The FDA's position is as follows:

"A verbal [oral] approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, it is acceptable to send the informed consent document to the legally authorized representative (LAR) by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it

is discussed. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical investigator by facsimile.”

RSRB approval of this process of consent will be limited to a case-by-case basis. Investigators wishing to conduct consent by telephone must clearly justify its rationale in the protocol.

Consent to Genetic Testing

New York State law requires the inclusion of specific language in consent forms for genetic testing research. Refer to the consent form template for genetic testing.

Waiver of Consent

The federal Common Rule regulations permit waiver of consent for research subjects provided the following criteria are met (note that waiver of consent is not permitted for FDA-regulated research):

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; *and*
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Waivers of Consent for Deception Research - Because subjects cannot truly consent without full information, the informed consent process is altered for approved studies involving deception. In their applications and study plans, investigators using deception should address the following points:

- Consideration of the scientific value and validity of the research
- Consideration of the comparative efficacy of alternative procedures
- Assurances that deception would not influence subjects' willingness to participate
- Provision of procedures for removing any harm through debriefing
- Assurances that the deception does not facilitate unwanted or inappropriate invasions of privacy
- Procedures for subjects who decline to give consent to the use of their information (i.e., data handling)

NOTE: Because deception research involves a waiver/alteration of consent, and the waiver/alteration may only be granted to studies involving minimal risk, deception studies may involve no greater than minimal risk.

Prior to data collection, subjects must have an opportunity to read and respond to information contained in a “Consent to Procedures,” which will include, at minimum, clear statements of:

- Study title
- Investigator names, department, and contacts
- What subjects will be asked to do
- Any risks associated with those activities
- Any payment or other reward for subject participation
- Unqualified opportunity to withdraw at any time without penalty
- Extension of the opportunity to ask questions and get answers

- Unless the study qualifies for a waiver of documentation of consent, the Consent to Procedures form will collect subject signature to the effect that the information has been read and understood

At the conclusion of participation, it is important that subjects be advised that deception has occurred, and be given the opportunity to withdraw or consent to have the data used. Subjects must have an opportunity to read and respond to additional information entitled, "Consent to Data Use" (see below), which will contain, at minimum, clear statements of:

- Study title
- Investigator names, department and contacts
- Full disclosure of the deception
- Unqualified opportunity to withdraw without penalty
- In addition, the following must be included:
- "This study involved deception. The study was reviewed and the federal requirement of informed consent was waived by the University of Rochester Research Subjects Review Board (RSRB)."
- "I give my permission for the investigators to use the data I provided in this study. If I withhold my permission, I understand that the data I provided will be destroyed."

Additional elements are on the "Consent to Data Use" and Consent to Procedures" found on the RSRB web site. [Research Subjects Review Board: Document Templates](#)

Alteration of the Consent Process/Document - The RSRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided:

- The research or demonstration project is to be conducted by or under the approval of state or local government officials and is designed to study:
 - Public benefit or service programs;
 - Procedures for obtaining benefits or services under those programs;
 - Possible changes in or alternatives to those programs or procedures; or
 - Possible changes in methods or levels of payment for benefits or services under those programs;
 - *and* the research could not practicably be carried out without the waiver or alteration.
 - *and* the research is not subject to FDA regulation.

Waiver of Documentation of Consent

The RSRB may also permit investigators to waive the requirement that the subject or the subject's authorized representative sign a written consent form if it finds either:

- that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context;
or,
- for non-FDA regulated studies, that the only record linking the subject and the research is the consent document and the principal risk is potential harm from breach of confidentiality. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written explanation about the research.

When it considers waiving the requirement to obtain written documentation of the consent process, the RSRB may require the investigator to provide subjects with a written description of the study. Refer to the consent form templates for an example of such an "information sheet" to provide to subjects. [Research Subjects Review Board: Document Templates](#)

Consent to Expanded Access or Single Patient Use

Sponsors and/or investigators may occasionally request RSRB review and approval of protocols using investigational drugs or devices in the clinical treatment of a patient or patients. Although this is still considered research under FDA regulations, consent wording for these activities differs from other research, in the following ways:

- The use of "patient" (vs. "subject") and "doctor" or "treating physician" (vs. investigator) is permitted.
- The compensation for injury section is deleted (unless the sponsor makes provision for such compensation).
- "Research study" is replaced with "treatment." (Note: the consent form must clearly indicate that the treatment is experimental/investigational/unproven.)

Charging Research Subjects for Drugs, Devices, Procedures and Services

The University of Rochester policy for charging research subjects for drugs, devices, biologics, procedures and services is based on the FDA regulations (21 CFR 312.7, 21 CFR 812.7), Medicare Reimbursement Regulations (42 CFR 413.90) and the FDA/HCFA Interagency Agreement #D95-2 (9/15/95). Per these regulations:

- No investigational drug, biologic or device may be charged to research subjects and/or their insurer without the prior written approval of the FDA.
- Research subjects and/or their insurer may not be charged for marketed or investigational drugs, biologics and/or devices when provided free of charge to the investigator.
- Research subjects and/or their insurer may be charged for professional and/or institutional services that would be considered usual and customary for the treatment and/or evaluation of medical conditions that are not reimbursed by the sponsor.
- Treatment for adverse events specifically related to a research activity, which was over and above usual patient care, should not be billed to the subject and/or their insurer.
- Any intention to charge the research subject and/or their insurer for a professional and/or institutional service, drug/biologic, or device provided to research subjects in the course of a study must be clearly indicated on the consent form, and approved by the RSRB.

Examples of this policy are:

When patients present for treatment or evaluation of medical conditions and also enroll in clinical trials that provide an alternative drug, device or procedure that does not materially change the course or cost of routine care, then the professional and/or institutional charges to the subject and/or insurer for such care is generally appropriate, as long as the costs of items/services have not been reimbursed or provided free through federal, state or private funds. For example:

- *A patient admitted for a surgical procedure that requires a preoperative antibiotic enrolls in a trial that substitutes a study antibiotic in place of the usual antibiotic. The new antibiotic is supplied by the sponsor. The medical and surgical care of the patient is otherwise unchanged. Because the provision of the experimental antibiotic does not materially change the delivery site or cost of care, the patient and/or insurer would be charged the traditional professional fees, but would not be charged for the drug. The billing code (DRG) may need to be adjusted to account for the free antibiotic.*
- *A patient is admitted for elective abdominal aortic aneurysm repair and agrees to enroll in the study of an investigational endovascular device rather than the traditional surgical approach. The device is not provided by the sponsor but is billed to the hospital. The procedure slightly lengthens the time in the operating room, but substantially reduces the intensive care unit stay. The site of care is unchanged for the treatment of this problem. Because the overall medical care is not materially changed in this example, the patient and/or insurer would be charged the usual fees.*

When patients enroll in a clinical trial that materially alters the basic care plan, site or cost of care, then customary charges to the subject and/or insurer may not be appropriate. The following examples illustrate this point:

- *A patient presents to the ambulatory department for treatment of herpes zoster. The normal course of treatment would be the use of an oral medication as an outpatient. The patient enrolls in a clinical trial of a new antiviral that requires hospitalization for two days and the intravenous administration of the drug. The hospitalization and intravenous drug costs are borne by the sponsoring agency. Because the care is significantly altered in terms of both the site and course, and because the charges are reimbursed by the sponsor, the subject and/or insurer should not be billed for any aspect related to this care.*
- *A patient admitted for surgical treatment of a lung malignancy enrolls in a protocol using an experimental radiation device in place of surgery. This new treatment requires 10 days in hospital care as opposed to the more traditional 5-6 days of care that would have been required for surgery. The radiation device is supplied by the sponsor, but there is no reimbursement by the sponsor for hospital care. Because the care plan and cost of care is significantly altered by the clinical study, the usual and other professional fees may not apply. Investigators should check with the Medical Center Compliance Office (273-1795).*

When patients who are enrolled in a clinical trial develop a medical condition specifically related to a research activity, then support for such treatment should be provided by the sponsor, where possible. Charges for such treatment should not ordinarily be billed to the subject and/or insurer. An example follows:

- *A patient who is enrolled in a clinical trial evaluating the efficacy of a ventricular antiarrhythmic agent requires a pacemaker per protocol (i.e., this is not standard care). Complications from the pacemaker placement require treatment in the emergency department. The sponsor provided for support for such treatment (i.e., complications from the clinical trial) in the contract. In this instance, the subject and insurer should not be billed for medical treatment that was a direct result of the research. (**Note:** such support should be included in the contract prior to initiation of the trial; however, there are a few exceptions to full indemnification [resource: ORPA – 275-4031]. Questions about patient billing may be referred to the Medical Center Compliance Office at 273-1795).*

There are several other examples that illustrate the inappropriateness of billing subjects and/or insurers for medical care rendered to patients enrolled in clinical trials. Of note, the most egregious form of inappropriately billing Medicare in the research context involves directly billing for the costs of items or services that are otherwise reimbursable (or free) to providers through federal or private funds. Submitting bills to Medicare for those items or services already paid for by other sources is an illegal double reimbursement for the same items or services.

Emergency Use of Unapproved Drugs and Medical Devices

Emergency use is defined as the use of an investigational drug, biological product or medical device with a human subject in a life-threatening situation in which no standard acceptable treatment is available [ref. 21 CFR 56.102(d)]. This does not include “off-label” uses of approved medical products in the practice of medicine (i.e., use not in a research context). In an emergency-use situation, the waiver of prior RSRB review and the waiver of consent may be permissible. Refer to [Appendix 3](#) for the form regarding Emergency Use of Experimental Procedures without RSRB Approval.

- **Waiver of RSRB Review** - The principal investigator is responsible for ensuring that research projects are conducted only after they have been given RSRB approval. Emergencies may arise in which an unapproved drug or device may offer the only life-saving alternative, but an Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) does not exist, the proposed use is not approved under an existing IND/IDE, or the physician or institution is not included under the IND/IDE.

The RSRB does not grant “approval” of emergency treatments, but rather acknowledges their occurrence and seeks to ensure that appropriate patient protection procedures are employed. The use and the outcome must be reported to the FDA.

Emergency use is the use of an investigational drug, biological product or medical device for a patient in a life-threatening situation in which no standard acceptable treatment is available. According to the FDA, “life-threatening” includes the scope of both life-threatening and severely debilitating, as defined below:

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potential fatal outcomes, where the endpoint of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the patients must be in a life-threatening situation requiring intervention before review at a convened meeting of the RSRB is feasible.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

The RSRB Office must be notified preferably before the emergency treatment is given but at least within five working days after it has occurred.

The physician will be asked to provide a written follow-up report on the treatment within five working days (see [Appendix 3](#) for the report). The emergency treatment will be reported to the next available meeting of the convened meeting responsible for the review of research conducted by the investigator’s department.

The emergency use provision is a **one-time** exception from RSRB approval. Any subsequent use of the test article must have RSRB approval (the physician’s report to the RSRB should indicate whether additional uses are anticipated. If so, a formal application for project review

should be submitted promptly so that an approved protocol will be in place before the next use occurs). Waiver of RSRB review under the emergency use provision does not automatically imply waiver of other human subject protections such as obtaining informed consent (see below). Other University offices/departments may also have a notification requirement.

NOTE: Safety information from emergency use cases should be reported to the FDA or the manufacturer as appropriate.

- ***Waiver of Informed Consent on a Case-By-Case Basis***

In a medical emergency, it may not be possible to obtain informed consent. Therefore, on a case-by-case basis, the requirement for prior consent may be waived if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

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

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

The subject and/or the subject's legal representative must be notified of the use of the experimental procedure and consent to continue should be obtained for those procedures requiring continued/repeat administration.

The investigator must notify the RSRB within five working days after the use of this waiver.

Consent through Oral Presentation and Short Written Form

When investigators anticipate enrolling even one subject who does not speak English, the RSRB requires a translation of the consent form into the language spoken by that subject. There are times, however, when an investigator may need to enroll a non-English-speaking subject who unexpectedly presents at the research site.

Here are the steps to take to take:

- Submit an amendment request to the RSRB (expedited review is permitted)
- Include a short-form written consent document that states, *in the subject's language*:
 - The title of the study;
 - That the consent for the research study was presented orally to the subject or the subject's authorized representative.
 - The presentation included the purposes, risks, benefits and alternatives (if any) of participation.

- That participation is voluntary. The subject does not have to take part and can withdraw at any time.
- That the subject was given a copy of the standard (English) consent form and a copy of the short form.
 - *And* name, signature line and date for the subject
 - *And* attestation, signature line and date for the witness

Ensure that the following issues have been addressed:

- The written consent document (standard English consent) states that the elements of disclosure required by regulations have been presented orally to the subject or the subject's authorized representative.
- The written summary (standard consent) embodies the basic and required additional elements of disclosure.
- There will be a witness to the oral presentation who is conversant in both English and the language of the subject (it is best if the witness is not a family member).
- The subject or the subject's authorized representative will sign and date the consent document.
- The witness will sign both the short form and a copy of the summary.
- The person actually obtaining consent will sign a copy of the summary.
- A copy of the short form will be given to the subject or the authorized representative.
- A copy of the summary will be given to the subject or the authorized representative.

An English version of the short form is included with the consent templates. Use this version to translate into the subject's language. The RSRB has examples of translated short forms, call 275-2398 for assistance.

APPENDIX 1

University of Rochester Policy on Enrollment of Adult Decisionally Incapacitated Research Subjects and Permission of Authorized Representatives

POLICY

It is the policy of the University of Rochester to permit authorized representatives to give permission for the enrollment of decisionally incapacitated adult subjects into certain research protocols in accordance with the terms and conditions specified below. This policy does not apply to the conduct of emergency research under Food and Drug Administration (FDA) regulations (21CFR50.24). This policy does not apply to the conduct of research with children.

BACKGROUND

Federal regulations (21CFR 50.20 and 45CFR46.116) allow a “legally authorized representative” (LAR) to give permission on behalf of a decisionally incapacitated adult subject, and defer to State law for the definition of an LAR. New York law (Public Health Law Article 24-A) allows LAR permission, but does not define the term “legally authorized representative.”

PURPOSE

The purpose of this policy and procedure is to provide additional protections for decisionally incapacitated adults who are enrolled into research studies. Therefore, it sets forth the circumstances under which the University will permit an authorized representative to allow enrollment into research on behalf of a decisionally incapacitated adult, and identifies those individuals who are considered to be authorized representatives.

BASIS for POLICY and PROCEDURES

The University of Rochester holds the ethical position that the use of surrogate permission with decisionally incapacitated adults should generally follow the federal regulations for research involving children (21CFR50 Subpart D and 45CFR46 Subpart D) and the protections they provide. Subpart D regulations limit the categories of approvable research in which children can be enrolled to the following:

- minimal risk (regardless of the likelihood of benefit to the children);
- greater than minimal risk research, if direct benefit to the children is anticipated;
- greater than minimal risk research with no direct benefit to subjects, but potentially yielding knowledge about the child’s disease/condition, however, the risk must be determined to present only a minor increase over minimal;
- other greater than minimal risk research in serious problem areas affecting children, but only after notices and additional reviews are accomplished.

Applying the above as a model, the University will permit enrollment of decisionally incapacitated adults, based on the permission of an authorized representative, into research that parallels the first three categories above. The University policy will not allow the enrollment of decisionally incapacitated adult subjects into research under the fourth (last) category above.

UNIVERSITY OF ROCHESTER PROCEDURES FOR APPROVAL OF STUDIES INVOLVING ADULT DECISIONALLY INCAPACITATED SUBJECTS

The following definitions are established for purposes of applying this policy:

- (a) “Capacity to consent” means an individual’s ability to understand and appreciate the nature and consequences of a proposed research procedure(s) or investigational

treatment, and to make an informed decision concerning participation in the research project.

(b) "Persons with Decisional Incapacity" are individuals who lack the ability to consent to procedures involved in the research because of inability to understand or process sufficient information about the study to reach a valid, self-directed decision about participation. Decisional incapacity may be temporary, permanent, progressive, or fluctuating.

(c) "Assent" means an affirmative agreement to participate in research given by a person with decisional incapacity. Failure to object is not assent and resistance to a research procedure in a non-verbal subject is an indication of dissent for that procedure.

(d) "Permission" means the agreement given by an authorized representative to the participation in research of a person with decisional incapacity. Such permission must be obtained in the same manner and extent as under the informed consent process for adults with capacity (i.e., sufficient information provided to the representative, adequate understanding of the information, and voluntary agreement to the enrollment).

(e) "Surrogate" or "Surrogate decision maker" means an authorized representative, such as a family member or guardian, who gives permission on behalf of a person with decisional incapacity.

(f) "Family member" means a relative or a friend with a close affinity i.e., individuals whose relationship with the person with decisional incapacity is equivalent to that of a family member. For purposes of this policy, the following are considered to be family members (listed in descending order of priority):

- A health care agent properly designated on a health care proxy form (See SMH Policy 9.3.1, Health Care Proxies);
- A court-appointed guardian or committee under the New York Surrogates Court Procedure Act Article 17-A;
- The spouse;
- An adult son or daughter;
- A parent;
- An adult brother or sister; or
- A close friend, who is an adult (18 years or older) who has a close personal relationship with the subject and provides a signed written statement, in a format approved by the RSRB, to the PI that he/she is a close friend of the subject, and that he/she has maintained such regular contact with the patient as to be familiar with the patient's activities, health, religious or moral beliefs and stating the facts and circumstances that demonstrate such familiarity.

(g) "Guardian" means an individual who is authorized under New York State law to give permission on behalf of persons with decisional incapacity to general medical care.

(h) "Authorized Representative" means an individual or judicial or other body authorized under New York State law (Public Health Law, Article 24 and other relevant law) to give permission on behalf of a prospective adult subject for the subject's participation in the procedure(s) involved in the research. The role of the authorized representative is to assist the subject as necessary in understanding the research procedures and to ensure that the subject's rights and welfare are protected. The following persons may act as authorized representatives for adults who have been determined to lack capacity (listed in descending order of priority):

- A health care agent properly designated on a health care proxy form (See SMH Policy 9.3.1, Health Care Proxies);
- A court-appointed guardian or committee under the New York Surrogates Court Procedure Act Article 17-A;
- The spouse;
- An adult son or daughter;
- A parent;
- An adult brother or sister; or
- A close friend, who is an adult (18 years or older) who has a close personal relationship with the subject and provides a signed written statement, in a format approved by the RSRB, to the PI or his/her designee that he/she is a close friend of the subject, and that he/she has maintained such regular contact with the patient as to be familiar with the patient's activities, health, religious or moral beliefs and stating the facts and circumstances that demonstrate such familiarity.

Categories of Research for Which Permission from an Authorized Representative Will Be Permitted When an Adult Subject Lacks Decision-making Capacity

Per University policy, research involving decisionally incapacitated adults must satisfy one or more of the conditions set forth below. The RSRB may, as an additional safeguard, obtain a consultation to assist the RSRB in assessing risk or reviewing the study and its procedures.

Category A - Research not involving greater than minimal risk

The RSRB may approve research that presents minimal risk if it finds and documents that:

- (b) inclusion will not adversely affect the rights and welfare of the subjects; and
- (c) adequate provisions are made for soliciting the consent of subjects who have the capacity to consent, and
- (d) adequate provisions are made for obtaining the assent of decisionally incapacitated adult subjects and the permission of their authorized representative(s) in accordance with this policy.

Category B - Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects

The RSRB may approve research that presents greater than minimal risk to adult subjects, but that has the prospect of direct benefit for subjects if the RSRB finds and documents that:

- (a) the risk is justified by the anticipated benefit to the subjects;
- (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) adequate provisions are made for soliciting the consent of subjects who have the capacity to consent, and
- (d) adequate provisions are made for obtaining the assent of decisionally incapacitated adult subjects and the permission of their authorized representative(s) in accordance with this policy.

Category C - Research involving a minor increase over minimal risk, with no prospect of direct benefit to individual subjects, but may produce knowledge about the subjects' disorder or condition

The RSRB may approve greater than minimal risk research that does not hold out the prospect of direct benefit for the individual subjects, if it finds that the research may produce knowledge about the subjects' disorder or condition, but only if the RSRB finds and documents that:

- (a) the risk represents a minor increase over minimal risk and the risk is justified by the anticipated benefit to persons with the subjects' disorder or condition, i.e., the importance of the knowledge to be gained by the research;
- (b) the research is reasonably similar to experiences in the subjects' actual or expected daily life including medical, dental, psychological and social situations;
- (c) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a problem affecting the health or welfare of the subjects;
- (d) adequate provisions are made for soliciting the consent of subjects who have the capacity to consent;
- (e) adequate provisions are made for obtaining the assent of decisionally incapacitated adult subjects and the permission of their authorized representative(s) in accordance with this policy; and
- (f) further review and concurrence from a senior institutional official who is not on the RSRB or on the research team.

Category C Research – Requirement for Institutional Review

For Category C research (minor increase over minimal risk, no direct benefit), an additional review and concurrence from the Senior Associate Dean for Research (for the School of Medicine and Dentistry) or designee, the Dean for Research (for the College) or designee, or the Dean of the principal investigator's school or designee will be required as a stipulation for RSRB approval. This additional review is to be performed in consultation with the University of Rochester Medical Center Office of Counsel and after the RSRB has found the study to be otherwise approvable, i.e., all other conditions and stipulations are met. The additional review is intended to ensure that only scientifically sound and institutionally supported research is conducted in Category C.

Additional Protections

In addition to limiting the categories of research for which permission of an authorized representative may be approved, the RSRB may, in its discretion, require additional appropriate mechanisms to further protect decisionally incapacitated adult subjects involved in research approved in any of the above categories. The choice of additional mechanisms depends upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their condition. For example, the RSRB may require:

- a screening procedure for cognitive impairment in at-risk populations
- a data monitoring committee or other formal study monitoring,
- continuing RSRB review more frequently than annually,
- consent monitors or the appointment of an advocate(s) for subjects, in addition to individuals acting as authorized representatives,
- capacity assessments and/or re-assessments from professionals who are not on the research team or the use of capacity assessment instruments. (Note: if upon reassessment, an adult subject regains capacity and expresses the desire to stop participation, that withdrawal must be honored.)

Requirements for Consent of Adult Subjects with Capacity or for Assent of Decisionally Incapacitated Adult Subjects and Permission of Surrogate

The RSRB will require that adequate provisions are made for soliciting the consent of each adult subject who is capable of giving consent. If an adult subject, who has been enrolled in research by the permission of a surrogate, regains capacity during the course of participation, then consent must be obtained from that person before continuing research-related activities. Research study designs must include appropriate procedures for the continuing/periodic capacity assessment of decisionally incapacitated adult subjects. The RSRB may waive the requirement for consent under the conditions required by 45 CFR 46.116 (i.e., minimal risk research). For FDA-regulated emergency use and emergent treatment studies, the procedures required by 21 CFR 50.23 and 24 are applicable.

Capacity Assessment

The permission of an authorized representative may only be used if an adult subject has been assessed as lacking decision-making capacity. All investigators are responsible for determining that potential subjects have the capacity to consent to research. Permission from an authorized representative may not be used for any adult subject who has the capacity to consent.

An adult subject is generally assumed to have the capacity to make an informed decision regarding research. In accordance with standard clinical procedures, a subject may be determined to lack capacity only if the ability to understand and appreciate the nature and consequences of enrolling in research, including the benefits and risks, the meaning of personal participation in the study, and to reach and communicate an informed decision is found to be deficient. The fact that a person has been determined to lack capacity to make other decisions (e.g., a conservator of the person's assets has been appointed) does not establish lack of capacity for a decision about research participation, nor does a determination of a lack of capacity to make a research enrollment decision mean that the person lacks capacity to make any other decision.

In studies involving a subject population whose capacity is known to be impaired, or is highly likely to be impaired, the study protocol must describe adequate procedures for making and documenting this determination. The study protocol/design must include procedures for informing persons who are determined to have decisional incapacity of that determination prior to enrollment in a study and procedures to document that this has occurred. Also, the study protocol/design must include procedures for informing subjects that they are to be enrolled in research with permission of an authorized representative. Such information should be given to subjects in the presence of the representative. Research study designs must include appropriate procedures for the continuing/periodic capacity assessment of decisionally incapacitated subjects.

Assent by Decisionally Incapacitated Adult Subjects

When an adult subject is not capable of providing consent, but is capable of providing assent, the research plan/protocol must describe adequate provisions for soliciting and documenting the assent of the subject in addition to obtaining the permission of the authorized representative. Assent of decisionally incapacitated adult subjects is required, unless specifically waived by the RSRB. Failure to object is not considered to be assent and resistance to a research procedure in a non-verbal subject is an indication of dissent for that procedure.

For minimal risk studies, the RSRB may waive the assent requirement under circumstances in which consent may be waived in 45 CFR 46.116. For FDA regulated studies, 21 CFR 50.23 and 24 apply. The RSRB may also waive the requirement for assent if it determines that it is not a necessary condition for protecting subjects because the capability of the subjects is so limited that they cannot reasonably be consulted (e.g., in coma or in an acute psychotic break). To the extent possible, given the subject's condition in these cases, the subject will be informed of the enrollment and the procedures involved. For all research, the adult subject's objection to

participation will be honored (i.e., the subject will not be enrolled into the research, or will be withdrawn from the research if already enrolled).

In determining whether assent will be required, the RSRB shall take into account the subjects' expected medical, social and psychological state. When the RSRB determines that assent is required, it will also determine whether, and how, assent must be documented.

Required Permission from an Authorized Representative for Adult Subjects Lacking Decision-making Capacity

When an adult subject does not have the capacity to consent, the investigator must solicit the permission of the subject's authorized representative, and may not enroll the subject or perform research activities until permission from the authorized representative is given. The identity of the authorized representative shall be noted in the research records. Permission of an authorized representative shall be documented in accordance with and to the extent required by 45 CFR 46.117 and 21 CFR 50.27.

The following persons may act as authorized representatives for adults who have been determined to lack capacity (listed in descending order of priority):

- A health care agent properly designated on a health care proxy form (See SMH Policy 9.3.1, Health Care Proxies);
- A court-appointed guardian or committee under the New York Surrogates Court Procedure Act Article 17-A;
- The spouse;
- An adult son or daughter;
- A parent;
- An adult brother or sister; or
- A close friend, who is an adult (18 years or older) who has a close personal relationship with the subject and provides a signed written statement, in a format approved by the RSRB, to the PI that he/she is a close friend of the subject, and that he/she has maintained such regular contact with the patient as to be familiar with the patient's activities, health, religious or moral beliefs and stating the facts and circumstances that demonstrate such familiarity.

When a person with priority on this list is not reasonably available, willing to make a decision, or competent to make a decision regarding research participation, the authority falls to the person of the next highest priority. Once identified, the identity of the surrogate shall be noted in the research records.

When the authorized representative is a family member and the research investigator learns that another family member on the list opposes the participation in the research to which the identified authorized representative has given permission, the subject will be discontinued from the research. An exception to this automatic withdrawal can be made by the investigator for research that is intended to be of direct benefit to the subject. In such case, the investigator may continue the subject's participation only if:

- the subject is deriving a reasonably evident direct benefit from participation;
- the individual opposing the enrollment is lower in priority on the list;
- the objecting individual does not provide facts or information demonstrating that participation in the research is detrimental to the subject's health or welfare or is contrary to the subject's previously expressed wishes; and
- the investigator notifies the RSRB of the plan to continue the subject's participation.

Upon notification, the RSRB may choose to take no further action (i.e., allow the subject to stay in the research) or may require the withdrawal of the subject. In reviewing the notification, the RSRB may consult with the URM Office of Counsel, the Strong Health Ethics Committee, and/or other appropriate sources of knowledge and expertise.

It is not the intent of this procedure to require investigators to seek out all family members. Rather, if these individuals self-identify themselves as valid family members and disagree with the participation, then the above process would come into effect.

Anticipated Loss of Decisional Capacity by Adult Subjects Enrolled In Research

In cases where adult subjects will be capable of providing consent to enroll, but will possibly or probably lose that capacity as the study progresses (e.g., in progressive dementia research), the study protocol must make provision for the subject to designate an authorized representative upon enrollment or at the earliest appropriate time while the subject still has capacity. In these cases, the subjects should be asked to provide guidance to the designated representative about the conditions under which the subject would and would not want to participate in the event of loss of capacity. Until/unless the subject loses capacity, the designated representative is not empowered to make decisions about the subject's participation in research.

Documentation

Documentation must be kept in the study records of the assessment of cognitive capacity, assessment of the capacity to consent, identification of the authorized representative, and consent, permission and assent as applicable.

Guidelines for Payment to Authorized Representatives

Generally speaking, it is not anticipated that any payment would be made to an authorized representative, however, reimbursement for direct costs incurred (e.g., parking and transportation) is permissible. A small payment for time lost – usually calculated at minimum wage rates – may also be permissible, however, no “incentive” payments to surrogates are permitted. In all cases, the study plan/protocol must clearly describe these payments, and the RSRB will determine their acceptability.

APPENDIX 2

**RSRB
Consent / Permission / Assent Guidelines**

Subject Age Range	Document Type(s)	Notes
7 and under	Parent Permission*	No assent script or form required
8 to under 13 years	Parent Permission* + Assent Script	<ul style="list-style-type: none"> • Age-appropriate • Verbal • Permits subject to opt out if parent(s) opt in • Signature of subject not required • Documentation of person obtaining assent
13 to under 18 years	Parent Permission* + Assent Form	<ul style="list-style-type: none"> • Age-appropriate • Written • Permits subject to opt out if parent(s) opt in • Signature of subject and person obtaining assent required
18 years and older	Consent form	<ul style="list-style-type: none"> • For subjects with decisional impairment, consult the UR Policy on Enrollment of Adult Decisionally Incapacitated Research Subjects • When a child reaches 18 while participating in a study, the appropriate consent process should be conducted for the now adult subject to consent to participate in the research for him/herself.
Under 18: treatment for life-threatening illness with possibility of direct benefit	Parent Permission	<ul style="list-style-type: none"> • Assent not required
Under 18: collection of sensitive information	Parent Permission* + Assent Form	<ul style="list-style-type: none"> • Parental permission may be waived (per University guidelines) • Documentation of consent may be waived
Under 18: children without parental supervision or for who parental permission is not a protection	Assent Form	<ul style="list-style-type: none"> • Parental permission may be waived (per University guidelines) • Appointment of advocate required

Per federal regulation:

- In determining whether children are capable of assenting, the RSRB will take into account the ages, maturity and psychological state of the children involved. The judgment may be made for all children involved in the research under a particular protocol, or for each child, as the RSRB deems appropriate.
- The assent of children is not a necessary condition for proceeding with the research if the RSRB determines that either of the following is true:
 - The capability of some or all of the children is so limited that they cannot reasonably be consulted.
 - The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well being of the children and is available only in the context of the research.

*UR Policy Exceptions (see UR Policy regarding Consent Issues involving Children):

1. Minimal risk research (e.g., anonymous surveys) with older adolescents (16-17 years [juniors or seniors in high school])
2. Purely observational studies of public behavior
3. studies of existing data
4. research with children in those circumstances where New York Law expressly gives children the right to seek certain types of medical treatment without parental consent.

APPENDIX 3

Report of Emergency Use of Experimental Procedure
Without RSRB Approval

Name of Physician: _____

Department: _____ Box# _____ Telephone # _____

Date of Treatment: _____

Use the checklist below to document emergency treatment:

	Yes	No
1. Was the patient in a life-threatening condition that needed immediate treatment?	<input type="checkbox"/>	<input type="checkbox"/>
2. Was there an acceptable, appropriate alternative to treatment?	<input type="checkbox"/>	<input type="checkbox"/>
3. Was there time to obtain FDA and/or RSRB approval?	<input type="checkbox"/>	<input type="checkbox"/>

Attach the following:

- A copy of the informed consent of the patient or the patient's authorized representative **or** written certification by yourself and a physician not otherwise participating in the emergency treatment that:
 - The patient was confronted by a life-threatening condition necessitating the use of the test article;
 - Informed consent could not be obtained because of an inability to communicate with, or obtain legally effective consent from, the patient;
 - Time was not sufficient to obtain consent from the patient's authorized representative;
 - No alternative method of approved or generally recognized therapy was available that provided an equal or greater likelihood of saving the patient's life.

Complete:

Description of use of investigational drug, biologic, device or other experimental procedure (Use attachments/additional pages as necessary):

Reason/justification for Emergency Use:

Patient response to treatment:

Description of Informed Consent process or Certification of Waiver:

NOTE: Waiver of informed consent is permissible only if both the investigator and a physician who is not otherwise participating in the investigation/use certify in writing all of the following: 1) the subject is confronted by a life-threatening situation necessitating the use of the test article; 2) informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; 3) time is not sufficient to obtain consent from the subject's legal representative; and 4) no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.]

Will an application for review of a research protocol to study this use will be forwarded to the RSRB for approval? _____ Yes _____ No (i.e., this use will not occur again)

Certification of Physician

I have complied with the requirements of the U.S. Food and Drug Administration regulations and the University of Rochester policy regarding this emergency use. I understand that subsequent use, either with this patient or with another patient requires RSRB review and approval.

Signature of Treating Physician

Date

Return completed form to: University of Rochester, Research Subjects Review Board Office, Medical Center, Room 1-6124, Box 315, 601 Elmwood Avenue, Rochester, New York, 14642

If you have any questions, please contact the RSRB Office at **(585) 275-2398**, Fax: **(585) 275-7896**.