# Midwest Health System IRB

# Institutional Review Board

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## *Principal Investigator's Procedure Manual*

## *for the*

## *Protection of Human Subjects in Research*

# INTRODUCTION

The Institutional Review Board (IRB) is responsible for the review and approval of the use of human subjects in research at Midwest Division. These guidelines provide an educational resource that can be used in the preparation and submission of research protocols, including informed consent documents, for review by the IRB. These guidelines are also designed to provide information on the ethical and legal responsibilities of investigators during the conduct of human subject research.

Complete copies of any referenced documents and forms are available in the Institutional Review Board Office, on disk, or through the Midwest Division web site http://irb.hcamidwest.com. As this investigator's manual cannot be expected to address every situation or question that might arise, Investigators are requested to contact the Institutional Review Board Staff (303-584-2300) to discuss such issues. Periodic updates or substantive changes will be made by the IRB as necessary and distributed to investigators.

Nothing in the IRB policies and procedures and/or the Federal regulations governing human subject research is intended to limit the authority of a physician or any other health care personnel to provide emergency medical care to the extent the individual is permitted to do so under applicable Federal, State or local law.

## BASIC PRINCIPLES

The research at Midwest Division is guided by the ethical principles regarding all research involving humans as subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report") and the Common Rule (45 CFR 46), regardless of whether the research is subject to Federal regulation or with whom conducted or source of sponsor support.

The first provision of the Nuremberg Code states that, "the voluntary consent of the human subject is absolutely essential." Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. Further, the following principles (as set forth in the Belmont Report), respect for persons, beneficence, and justice, are the three quintessential requirements for the ethical conduct of research involving human subjects.

- Respect for persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.
- Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.
- Justice requires that the benefits and burdens of research be distributed fairly.

## Midwest Division's IRB POLICY

Midwest Division's IRB has provided a formal guarantee (Federal Wide Assurance - FWA00002948) to the US Department of Health and Human Services that it will follow procedures which will assure the protection of all human subjects involved in any research project sponsored by or undertaken by Midwest Division regardless of sponsorship. This guarantee applies to all human subject research conducted by anyone on the premises of Midwest Division and to research conducted elsewhere by its employees in connection with their institutional responsibilities.

Except for those categories of research specifically exempted, all proposed research protocols will be reviewed and approved by the IRB in accordance with established procedures. The use of human subjects in research will not be permitted until the IRB has reviewed and approved the research protocol and informed consent has been obtained from the subject or the subject's legal representative.

the subject population. Factors such as the required number of subjects, age range, sex, ethnic background and health status will be considered. The utilization of any vulnerable classes of subjects, such as fetuses, prisoners, children, and mentally incompetent persons, must be clearly justified. Although the use of vulnerable persons as subjects is not prohibited by any regulations or ethical codes, justification for their involvement in research generally becomes more difficult as the degree of risk and vulnerability increases.

Naturally, there are exceptions to the principle of "equitable selection of subjects." For instance, research involving the study of a disease which is prevalent in only one ethnic or racial group (e.g., sickle cell anemia and Tay-Sachs Disease) would not require the application of this principle.

In past years, the standard has been to exclude populations from participation in research activities when there is no evidence of safety in those populations. For example, pregnant women have been largely excluded from research because there is seldom safety data available for pregnant women and fetuses.

Under the new NIH/OHRP policies, it has been made very explicit that if participation in research may benefit a potential subject, then that person must be given the opportunity to participate. At Midwest Division, we are asking that every blanket exclusion of particular populations from potentially beneficial studies be justified based on data from the literature on the drug/device/procedure being studied. It is important to note that the absence of data confirming safety is not equivalent to the presence of data confirming risk.

The following are some ideas to think about when excluding certain populations from your research studies:

(1) Is the potential benefit to the subject great enough that the exclusion of a class of subjects is a matter which raises serious justice concerns?
(2) Is the importance of the information to be gained from the study (and its future applicability to the population being excluded) a matter which raises justice and/or safety concerns?
(3) In the absence of known risk, is serious risk reasonably inferred from similarities between the drug/device/procedure being studied and other drugs/devices/procedures? Safety data from chemical analogues of the drug under investigation may have some bearing on the determination of risk.
(4) If there is a reasonably inferred risk, are the likelihood and severity of that risk (and absence of benefit) so striking as to make it appropriate to usurp the subject's usual role as decision-making authority with regard to risk?

## REVIEW OF METHOD(S) OF SUBJECT RECRUITMENT

The IRB will review the method of prospective subject identification and recruitment in order to be assured that it is ethically and legally acceptable. Advertisements used to recruit subjects are considered an extension of the recruitment and informed consent processes and, therefore, must be reviewed and approved by the IRB.

### Screening Tests Prior to Study Enrollment

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of or in preparation for the research, it is part of the research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for

research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

## REVIEW OF EXPERIMENTAL DESIGN

While the IRB is not charged by Federal regulation with the responsibility of reviewing protocols for scientific merit, issues related to the adequacy of the scientific design often emerge during the review. Such issues as inclusion of adequate and appropriate controls, adequacy of sample size, and appropriateness of experimental endpoints may be raised in the review. The IRB believes it is necessary to make a judgment on the validity of the study design as part of its assessment of the risk/benefit ratio, because no risk to subjects can be justified ethically if the study design is flawed to the degree that no useful information is likely to be forthcoming.

In reviewing any protocol, the IRB should be provided with complete information regarding experimental design and the scientific rationale (including the results of previous animal and human studies) underlying the proposed research, and the statistical basis for the structure of the investigation.

### Deception of Research Subjects

It should be noted that while the IRB accepts the need for certain types of research to employ strategies that include either deception and/or withholding of information, use of such strategies must be fully justified. In general, deception is not acceptable if in the judgment of the IRB the subject would have declined to participate had the subject been informed of the true purpose of the research. For example, investigational drug studies, which require a "washout period", during which the subject is given a placebo rather than his/her regularly prescribed drug, must generally be so informed.

Midwest Division strongly encourages its researchers using deception to employ the following American Psychological Association guideline:

(1) Apply a cost-benefit analysis that explicitly considers the potential for harm created and/or exacerbated by the use of deception,
(2) Consider alternative methodologies, and
(3) Fully explain the nature of the deception at the conclusion of the study or explicitly justify withholding such information.

In all cases, the safety and comfort of the subjects should be of paramount concern.

When evaluating the use of deception in research, the IRB will discuss the following issues:

(1) Validity of the research,
(2) Alternative methodologies,
(3) The characteristics, values, and morals of the experimental sample,
(4) Potential harm,
(5) Privacy and confidentiality, and
(6) Informed consent.
    a. Although subjects may not be fully informed, they should be informed of as much as possible without threatening the ability of the researcher to test the true hypothesis of the study.
    b. Midwest Division's recommendation is that the consent form should:
        1. Never be used as part of the deception and thus should not include anything that is untrue, and
        2. Reveal as much as possible to the participant regarding the procedures in the study.
        3. The consent form does not need to detail specific elements of the study if this will eliminate the capability of the study to inform the process under investigation.

## REVIEW OF THE POTENTIAL RISKS

Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the policies of Midwest Division and existing federal regulations. One of the major responsibilities of the IRB, therefore, is to assess the risks and benefits of proposed research.

Risk is a potential harm (injury) associated with the research that a reasonable person, in what the investigator knows or should know to be the subject's position, would be likely to consider significant in deciding whether or not to participate in the research. The concept of risk includes discomfort, burden, or inconvenience a subject may experience as a result of the research procedures. Underlying the consideration of risk is the implicit moral guideline that all investigators have a duty to not harm their subjects and must minimize potential risk to the greatest extent possible.

In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies subjects would undergo even if not participating in research, will be considered. For example, if the research is designed to measure the behavioral results of physical interventions performed for therapeutic reasons (e.g., effects on memory of brain surgery performed for the relief of epilepsy), then only the risks presented by the memory tests will be considered when the IRB performs its risk/benefit analysis. It is possible for the risks of the research to be minimal even when the therapeutic procedure presents more than minimal risk. Midwest Division's IRB will recognize, however, that distinguishing therapeutic from research activities can sometimes require very fine line drawing. Before eliminating an activity from consideration in its risk/benefit analysis, the IRB will be certain that the activity truly constitutes therapy and not research.

It is important to recognize that the potential risks faced by research subjects may be posed by design features employed to assure valid results as well as by the particular interventions or maneuvers that may be performed in the course of the research. Subjects participating in a study whose research design involves random assignment to treatment groups face the chance that they may not receive the treatment that turns out to be more efficacious. Subjects participating in a double-masked study take the risk that the information necessary for individual treatment might not be available to the proper persons when needed. In behavioral, social, and some biomedical research, the methods for gathering information may pose the added risk of invasion of privacy and possible violations of confidentiality. Many risks of research are the risks inherent in the methodologies of gathering and analyzing data, although the more obvious risks may be those posed by particular interventions and procedures performed during the course of research.

The five major types of risk are:

(1) Physical risk (e.g., pain, bruising and infection associated with venipuncture, adverse reactions to drugs, muscle soreness and pain as a consequence of exercise testing, heart attack induced by maximal exercise test);
(2) Psychological risk (e.g., depression and confusion as a result of administration of drugs, feelings of guilt precipitated by a sensitive survey);
(3) Social risk (e.g., invasion of privacy, loss of community standing);
(4) Legal risk (e.g., criminal prosecution or revocation of parole); and
(5) Economic risk (e.g., loss of employment, loss of potential monetary gain).

Possible risks within qualitative social science research include the following:

(1) Breach of confidentiality, whether actual or potential
(2) Violation of privacy, even when confidentiality is assured
(3) Validation of inappropriate or undesirable behaviors of subjects, perhaps based on misunderstanding of

the researcher's intent
(4) Presentation of results in a way that does not respect the subjects' interests
(5) Possible harm to individuals not directly involved in the research, but about whom data are obtained indirectly (secondary subjects), or who belong to the class or group from which the subjects were selected
(6) Harm to subjects' dignity, self-image, or innocence as a result of indiscreet or age-inappropriate questions in an interview or questionnaire

**Minimal Risk vs. Greater Than Minimal Risk**

Minimal risk is broadly defined as the probability of and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life [of the proposed study subjects -- may be broadened if approved by the IRB] or during the performance of routine physical or psychological examinations or tests (e.g., collection of urine, collection of sweat, weighing, pulse measurement, voice recordings, electrocardiography). It should be noted that there is no definition of "greater than minimal risk."

The definition of minimal risk for research involving prisoners differs somewhat from that given for non-institutionalized adults. Minimal risk for prisoners, "is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.**"**

Once the risks have been identified, the IRB will assess whether the research presents greater than minimal risk. The IRB may use the expedited review process for proposals, which meet certain conditions (the research must present no more than minimal risk and the involvement of human subjects must fall into one or more categories as outlined, in the Expedited Review section).

On average, if the IRB determines that a research study is minimal risk, then it will be reviewed annually, and if the IRB determines that a research study is greater than minimal risk, then it will be reviewed every six months. The approval letter that is sent to the investigator following the IRB approval of the study will note the risk classification and how often it will be reviewed by the IRB.

In research presenting more than minimal risk, potential subjects must be informed of the availability of medical treatment and compensation in the case of research-related injury, including who will pay for the treatment and the availability of other financial compensation.

**Determination That Risks Are Minimized**

Risks, even when unavoidable, can be reduced or managed. Precautions, safeguards, and alternatives can be incorporated into the research activity to reduce the probability of harm or limit its severity or duration. The IRB is responsible for assuring that risks are minimized to the extent possible.

Midwest Division's IRB will analyze the beneficial and harmful effects anticipated in the research, as well as the effects of any treatments that might be administered in ordinary practice, and those associated with receiving no treatment at all. In addition, they will consider whether potentially harmful effects can be adequately detected, prevented, or treated. The risks and complications of any underlying disease that may be present must also be assessed.

Some examples of minimizing risks in a behavioral study are the following:
(1) Risk of a breach of confidentiality of the data: obtaining a Certificate of Confidentiality; use of unique identifiers; use of locked research file cabinets; etc.
(2) Risk of subject becoming upset in response to a sensitive interview/questionnaire: having a counselor on call, in case the subject would like to talk about his/her feelings.

## REVIEW OF POTENTIAL BENEFITS

A benefit is a valued or desired outcome. Benefits associated with participation in research can be classified generally as those that accrue to the subject directly (e.g., improvement of the subject's health status, acquisition by the subject of knowledge considered of value) and those that accrue to society (e.g., additions to the knowledge base). The IRB will review the anticipated benefits to both the subject and to others. In addition, the IRB will consider whether the benefits are maximized to the greatest extent possible through proper protocol design. Therefore, an underlying moral notion of beneficence should guide the investigator.

Financial or other forms of compensation are not considered a benefit to be derived from research participation. Although the subject may consider financial compensation a desirable outcome, this fact will not be used in the risk-benefit analysis.

## RISK-BENEFIT ANALYSIS

Once the potential risks and benefits are identified, an ethical review of research requires an examination of the relationship of the risks to the benefits. Risks and benefits cannot be considered parallel constructs and, therefore, no formula is applicable. The various ethical codes and regulations, however, require a favorable balance between harm and benefit. To assist the investigator and the IRB in assessing the risk-benefit relationship, the following is a series of principles, which take into consideration whether or not the research is therapeutic in nature.

(1) In research that has no likelihood or intent of producing a diagnostic, preventive or therapeutic benefit to the subject (non-therapeutic research), the potential risk to the subject must be outweighed or balanced by the potential benefit to the subject and/or by the potential benefit to society.
(2) In research involving the study of the efficacy of a therapeutic or diagnostic method and the intervention is, therefore, not designed solely to enhance the well-being of the subject who is seeking a health benefit (therapeutic research), the potential risk should be primarily outweighed or balanced by the potential benefit to the subject. In addition, the relationship of the potential benefit to the risk must be at least as favorable to the subject as that presented by alternate standard therapies available to the subject in the non-research context. No subject is allowed to continue participating in a research protocol if therapy of proven superior nature becomes available to the subject.
(3) In research where a standard therapy not part of the research protocol is employed solely for the benefit of the subject along with additional procedures performed solely for research purposes, the potential benefits of the therapy must not be used to justify exposing subjects to the risks associated with the research procedures. Such risks can only be justified in light of the potential benefits of the research procedures. Conversely, only the risks associated with the research procedures should be used in determining the risk-benefit ratio.

## REVIEW OF PROPOSED SUBJECT COMPENSATION

The IRB will review the amount of compensation (monetary as well as other forms), and schedule of all payments in order to be assured that neither are coercive or present undue influence. Actual/estimated costs, such as for transportation and child care, may be the basis for payments to the study subjects.

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such incentive is not coercive. The IRB will determine that the amount paid as a bonus for completion is 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 payment(s), should be set forth in the informed consent document.

## REVIEW OF CONFIDENTIALITY

The IRB will review the methods to be used to preserve confidentiality. If research data with subject identifiers will be made available to persons other than the listed investigators, sponsor or federal agency, the IRB will review the justification for sharing this data and determine acceptability.

### Certificates of Confidentiality

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality 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. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

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

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

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

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

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

Certificates do not authorize researchers to refuse to disclose information about subjects if authorized DHHS personnel request such information for an audit or program evaluation. Neither can researchers refuse to disclose such information if it is required to be disclosed by the Federal Food, Drug, and Cosmetic Act.

In the informed consent form, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a Certificate is in effect.

It should be noted that Certificates of Confidentiality do not take the place of good data security or clear policies and procedures for data protection, which are essential to the protection of research participants' privacy. Researchers should take appropriate steps to safeguard research data and findings. Unauthorized individuals must not access the research data or learn the identity of research participants.

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. NIH provides detailed instructions for investigators wishing to make an application. Detailed application instructions, and additional information can be found on NIH's web site, at http://grants1.nih.gov/grants/policy/coc/.

Investigators planning to apply for a Certificate of Confidentiality should inform the IRB of this at the time of the protocol's initial review. If an investigator has not stated his/her intent to apply for a Certificate of Confidentiality, and the IRB deems that one is necessary, it will grant an approval contingent upon the receipt of the Certificate of Confidentiality.

A copy of the Certificate of Confidentiality should be forwarded to the IRB office upon receipt.

## REVIEW OF INFORMED CONSENT

Although there are federal guidelines requiring the subject or the subject's legally authorized representative to give consent prior to the subject's participation in an experiment, the principal reason for informing subjects about an experiment is that they have a moral right to know what is to be done to them and what risk this entails before they give their consent. Human beings are considered autonomous and the requirement of informed consent is designed to uphold the ethical principle of "respect for persons." The use of human subjects is a privilege -- a favor -- granted to the experimenter, rather than a right. An experiment is something that is done to the subject and therefore differs from the usual medical practice where something is done solely for the patient.

In order for consent to be ethically and legally valid, it must meet the requirements stated in Principal I of the Nuremberg Code and the informed consent section of the Federal regulations (45 CFR 46.116 and 21 CFR 50.20) which is based, in part, upon the Nuremberg Code. Principle I of the Nuremberg Code states, "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understandable and enlightened decision."

The legal documentation of informed consent is the consent form signed by the subject, the investigator or person obtaining consent, and a witness (if required). The ethical and, indeed, legal validity of consent is, however, dependent upon the process of informed consent which requires the investigator to engage in dialogue or negotiation with the prospective subject. The consent form, therefore, should be used by the investigator as an instrument to guide the negotiations with the prospective subject. The informed consent form must embody the elements of informed consent contained in the HHS and/or FDA regulations. The IRB will review both the consent form and the process of informed consent to ensure its acceptability.

The basic elements of the consent process, as detailed below, include:

(1) Full disclosure of the nature of the research and the subject's participation,
(2) Adequate comprehension on the part of the potential subject, and
(3) The subject's voluntary choice to participate.

In most research activities, an informed consent must be obtained by the investigator or his/her designee from each of the participants; or, in the case of those not able to give consent (e.g., children, mentally retarded), consent must be obtained from their guardians or legal representatives. A copy of the informed consent should be given to the person signing the form. The IRB must approve all consent documents and copies of such will be kept on file by the IRB.

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative, and should be written at a sixth grade reading level. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

In clear and non-technical language, subjects must be informed of:

(1) The fact that the study is research.
(2) The purposes of the research.
(3) The expected duration of the subject's participation.
(4) The procedures to be followed, whether there will be hospitalization to receive treatments, statements regarding medical procedures that will be performed and whether any are experimental. Include how many treatments will be given, how often and over what period of time.
(5) Any reasonably foreseeable risks or discomforts.
(6) The benefits to the subject or to others, which may reasonably be expected from the research.
(7) Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
(8) The extent to which confidentiality of data and privacy of subjects will be maintained.
(9) For research involving more than minimal risk, whether any medical treatments are available if injury occurs or whether there is any compensation for injury, and if so, what they consist of, or where further information may be obtained.
(10) Whom to contact for answers to pertinent questions about the research, subjects' rights, and research-related injury to the subject. Include complete phone numbers and contact persons for various categories (about the specific study or about patient rights in general) of information that may become important to the subject at a later date. The contact for research subjects' rights should be the local IRB Chairperson.
(11) The fact that participation is voluntary and that the subject may withdraw his or her consent at any time without penalty or loss of benefits.

The following additional elements of information shall also be provided to each subject, when appropriate:

(1) A statement that the particular treatment or procedure may involve risks to the subject, (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
(2) A statement that there are circumstances under which the subject may be terminated from participation by the investigator without the subject's consent such as when the subject does not follow the given instructions given to them.
(3) A description of additional costs that may result from participation in the research, noting that some insurance carriers may not pay for care that is delivered in a research context.
(4) An explanation of any consequences of a subject's voluntary withdrawal from the research and procedures for orderly termination of participation by the subject to protect the welfare of the subject.

(5) A statement that the subject will be notified of any significant new findings developed during the course of the research which may influence the subject's willingness to continue participation.
(6) Indicate the approximate number of subjects involved in the study.

Other general guidelines to preparing informed consent documents:

(1) The use of the wording "I Understand" is inappropriate since most subjects will not understand the scientific and medical significance of all the statements. Also statements such as "This study has been fully explained to me" or "I fully understand the study" are inappropriate since the subjects cannot certify completeness of disclosure.
(2) Use of the first person can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence over a subject.
(3) Use of scientific jargon and legalese is not appropriate.
(4) No unsubstantiated claims of effectiveness or overly optimistic representations should be included.
(5) Payments to the subjects should accrue as the study progresses and should not be an amount that could be considered coercive. The amount and schedule of payments should be submitted to the IRB for approval.
(6) FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.
(7) Phrases such as "FDA has given permission" or "FDA has approved" should not be used.
(8) FDA explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. HHS regulations do not explicitly require consent forms to be dated.
(9) When the study subject population includes non-English speaking people, or if the Investigator has reason to believe the subject does not fully comprehend English, or if the consent interviews will be conducted in another language other than English, the IRB requires a translated consent document. A non-English speaking subject should receive a copy of the translated document.
(10) A person who speaks and understands English, but does not read and write, can enroll by "marking their mark" on the consent document. An impartial witness should attest to the adequacy of the consent process and that the subject voluntarily agrees.
(11) For research with children, children about the age of 8 or 9 and above should sign assent; full consent is signed by the parent or legal guardian (please see the section on IRB Special Review Considerations – Research Involving Children, for more information regarding assent and consent for this population).
(12) While most individuals assume that therapists and teachers act in the patient's or student's best interest, evidence has indicated that this assumption persists even if the subjects are told that the activity is research and will have no direct benefit for them. Therefore, special care must be taken in these settings to ensure that the potential subjects understand the nature of the research.

No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence (45 CFR 46.116).

Examples of exculpatory language include the following:

- By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.
- By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
- I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.

Examples of acceptable language include the following:

- By consenting to participate, you authorize the use of your bodily fluids and tissue samples for the research described above.

- This hospital is not able to offer financial compensation nor to absorb the costs of medical treatment should you be injured as a result of participating in this research.
- This hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge.

**Documentation of Informed Consent**

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative, and the person obtaining consent. A copy shall be given to the person signing the form. The consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent listed above. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the required elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

Subjects who do not speak English: Where informed consent is documented using this short form procedure for non-English speaking subjects, the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the convened full IRB has already approved the protocol, the full English language informed consent document, and the English version of the short form document.

With appropriate justification, the IRB may waive the documentation requirement for informed consent (45 CFR 46.117). Investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (note that FDA does NOT provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies, which would fall into that category of research); or

(2) 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 of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

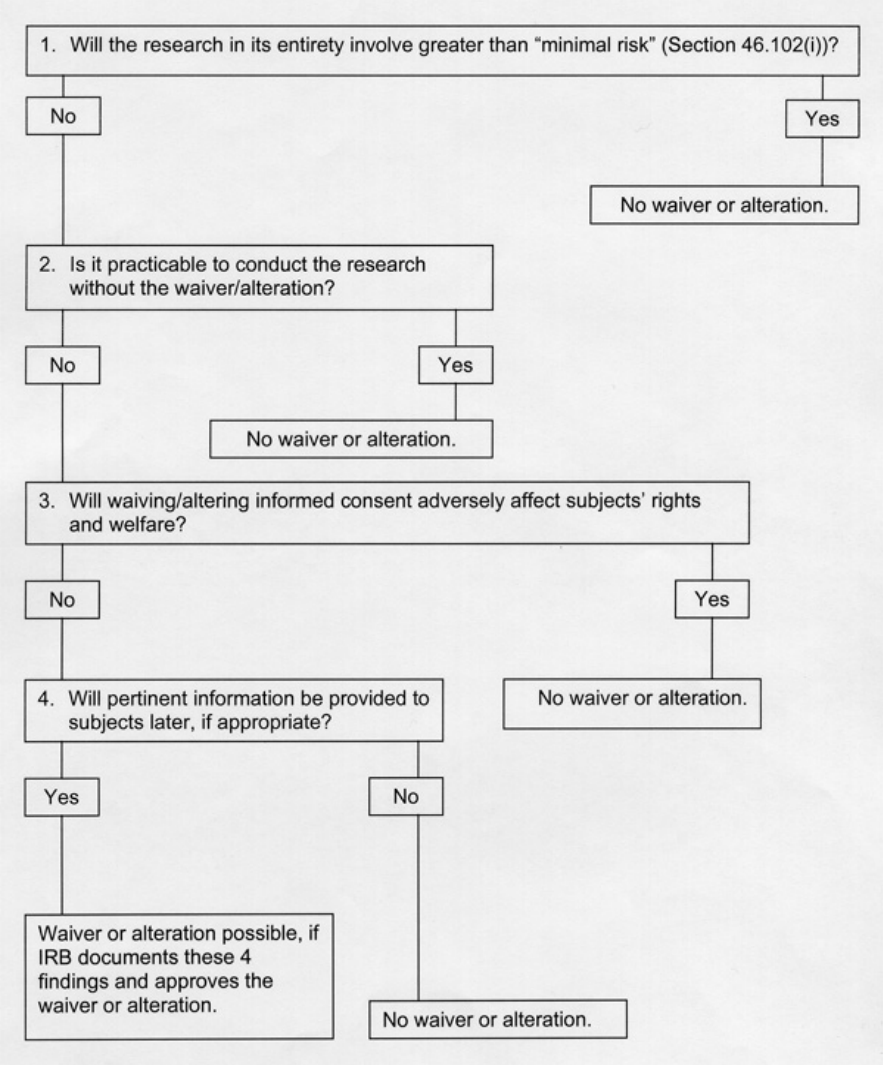
**Informed Consent Alterations and Waivers**

With appropriate justification, the IRB may waive the requirement for informed consent (45 CFR 46.116 (d)). Investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

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

Investigators may use the following OHRP Decision Chart to help determine if the IRB can employ 45 CFR 46.116(d) to waive informed consent or alter informed consent requirements:



FDA provides for an exception from the informed consent requirements only in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in 20 CFR 50.23. FDA has no other provision for waiving or altering elements of informed consent under certain conditions, because the types of studies, which would qualify for such waivers are either not regulated by FDA.

**FDA Exception From Informed Consent Requirement: Emergency Use**

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

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

If, in the investigator's opinion, immediate use of the investigational drug or device is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the investigational drug or device [21 CFR 50.23(c)].

**FDA Exception from Informed Consent Requirements for Emergency Research**

For FDA regulated studies, the informed consent requirements can only be waived if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following for emergency research:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
(2) Obtaining informed consent is not feasible because:
    a. The subjects will not be able to give their informed consent as a result of their medical condition;
    b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
    c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
(3) Participation in the research holds out the prospect of direct benefit to the subjects because:
    a. Subjects are facing a life-threatening situation that necessitates intervention;
    b. Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
    c. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.
(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
    b. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
    c. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
    d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
    e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The investigator (and ultimately the IRB) is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

Protocols involving an exception to the informed consent requirement must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the above-mentioned criteria or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA.

**Cognitively Impaired Subjects**

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a reassessment of decision-making capacity.

**Use of Facsimile or Mail to Document Informed Consent**

In rare circumstances, depending upon the design of a study, the IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the potential subject or the potential subject's legally authorized representative and to conduct the consent interview by telephone when the subject or the legally authorized representative can read the consent document as it is discussed. The consent document must be returned to the Investigator with the signature of the subject or subject's legally authorized representative, by mail or facsimile, before any research procedures may be implemented. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

## AUDIOTAPING, VIDEOTAPING, AND STILL PHOTOGRAPHY

Investigators' plans for recording data should receive prospective IRB review and be included in the informed consent process. Plans to destroy, share, or archive the recordings should also be discussed with the IRB and with study participants. If an investigator chooses to archive recordings but obscure the identities of participants in publication, then plans for protecting the confidentiality of the original study records must also be addressed.

Occasionally, although investigators prefer to record or photograph participants, they state that they could carry out their research without such recordings. In these cases, participants should be provided with an opportunity to consent or decline to consent to recordings. This may be assured by providing separate consent forms, one to participate in the research, and one to participate in the recordings.

## REVIEW OF INVESTIGATOR QUALIFICATIONS

The IRB will review investigator qualifications and must be assured that:

(1) The investigator has the appropriate qualifications and licensure to carry out the procedures involving human subjects with an acceptable degree of risk, and
(2) The investigator has adequate facilities to conduct the research with an acceptable degree of risk.

## STATE LAWS

Every state has its own statutes, regulations, and case law that may impose requirements on the research process that add to or are different from what federal law requires. Although some federal laws in essence "overrule" conflicting state laws, this is generally not the case with state laws relating to the research process. These laws vary considerably from state to state.

The IRB will review the following, to make sure that the protocol is consistent with state regulations:

(1) Age of consent
(2) Capacity to consent/legally authorized representative
(3) Children's assent
(4) Informed consent
(5) Genetic research
(6) Confidentiality of medical records

(7) HIV/STD reporting requirements
(8) Laws about referral fees and recruitment methods
(9) Laws governing clinical research
(10) Laws about investigational drugs
(11) Laws about vulnerable patients
(12) Laws about medical practice and delegation of authority to perform procedures.

Investigators should contact their state department of health, an attorney experienced in health care law, or their local IRB department if they are unsure of pertinent state laws.

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## IRB SPECIAL REVIEW CONSIDERATIONS

## RESEARCH INVOLVING CHILDREN

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children. Research that is contrary to the rights and welfare of child-subjects is prohibited.

Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted", 45 CFR 46.402(a).

**Analysis of Probable Risks, Possible Benefits, and Associated Discomforts**

The IRB review of research involving children as subjects will consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB will weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

Federal regulations require the IRB to classify research involving children into one of four categories and to document its discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by the IRB, based on degree of risk and benefit to individual subjects, are as follows:

(1) Research not involving greater than minimal risk.
(2) Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach.
(3) Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(4) Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research that is not approvable under the above three categories may be conducted provided that the IRB (and, if funded by DHHS, the Secretary after consultation with a panel of experts) finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles.

In all cases, the IRB will determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians.

Central to the IRB's consideration of research involving children is the determination of what constitutes minimal risk. Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The assessment of the probability and magnitude of the risk, however, may be different in sick children and may vary depending on the diseases or conditions the subjects may have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, the IRB may consider that children suffering from chronic illnesses who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences. The IRB will also consider the extent to which research procedures would be a burden to any child, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed the limits of minimal risk may be difficult to define in the abstract, but should not be too difficult to identify on a case-by-case basis. Riskier procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress may also exceed minimal risk.

In assessing the possible benefits of research intervention, the IRB will consider the variability in health statuses among potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or a toxin (e.g., meningococcus or lead) where it is known that a percentage of the children exposed will actually experience untoward consequences. A child may also be in an early state of disease, e.g., an HIV-infected child, or may actually suffer from disease or other significant medical condition. Thus the IRB will take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

The issue of Phase 1 drug studies deserves special consideration. The usual approach to designing drug studies involving children as subjects is for appropriate studies to be conducted first in animals, adults, and older children before young children are involved as research subjects. There are some studies, however, in which data may not be entirely generalizable from older populations, and in which the existence of life-threatening conditions for children are important considerations in the IRB's risk/benefit analysis. The requirement for previous testing in adults or older children may thus not be appropriate. Furthermore, some diseases specific to children may require that children be involved without data from older groups (e.g., there is no adult model that mimics the state of HIV-infected newborns; Wilms' tumor and various cancers such as neuroblastoma affect infants who do not survive into older childhood.) In some cases "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacologic safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.

**Consent Process**

When children or minors are involved in research, the regulations require the assent of the child or minor and the permission of the parent(s), in place of the consent of the subjects.

Given that children have not reached their full intellectual and emotional capacities and are legally unable to give valid consent, involving children in research requires the permission of their parents or legally authorized representatives. The IRB will determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered "not reasonably available" (examples of circumstances in which parental permission may be inappropriate are discussed below). In addition, the IRB will determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Category 1, minimal risk research, or Category 2, research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects. Where research is covered by Categories 3 and 4, and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

While children may be legally incapable of giving informed consent, they nevertheless may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. The IRB must determine for each protocol - depending on such factors as the nature of the research and the age, status, and condition of the proposed subjects - whether all or some of the children are capable of assenting to participation. Where appropriate, the IRB may choose to review on a case-by-case basis whether assent should be sought from given individual subjects. While assent is not required to be sought from children starting at a specific age, assent will be sought when, in the judgment of the IRB, the children are capable of providing their assent, taking into account the ages, maturity, and psychological state of the children involved.

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, the IRB will be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

When the IRB determines that the assent of the child is required, it will also determine that the provisions for obtaining and documenting assent are adequate. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate.

For some research activities, the IRB may require that either an IRB member or an advocate for the child be present during the assent and permission procedures to verify the child's understanding and to support the child's preferences. The IRB may also require that the parent(s) or a close family member be present during the research, especially if a young child will be exposed to significant discomfort or inconvenience, or if the child will be required to spend time in an unfamiliar place.

The requirement for parental permission may be inappropriate in some cases. Examples include research involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (e.g., treatment for venereal disease, drug abuse, or emotional disorders). In other research (e.g., research on child abuse or neglect), there may be serious doubt as to whether the parents' interests adequately reflect the child's interests. In these types of cases, the IRB will consider the development of alternative procedures, on a case by case basis, for protecting the rights and interests of the children asked to participate, including, perhaps, the court appointment of special guardians.

Parental permission may sometimes be insufficient to protect the child's interests. In cases involving transplants (e.g., of bone marrow or a kidney) between minor siblings, the parents' concern for the afflicted child may interfere with their consideration of the best interests of the healthy donor. Therefore, the IRB may consider other alternatives, such as asking for court review of the parents' decision.

The IRB will consult legal counsel about the applicability of any state laws affecting consent for the proposed research. The IRB will make itself aware of the age of majority in the state as well as laws or court decisions that might limit the right of parents to consent on behalf of their children in certain circumstances. Age and conditions of emancipation will differ from state to state. In some states the age at which a child can give consent to medical care differs depending on the medical condition involved (e.g., venereal diseases). The federal regulations require that all research activities must comply not only with the regulations but also with the law of the state in which they are performed.

**Exemption From Review**

The exemption (see exemption category 2 under Exemptions from IRB Review), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed. The remaining exemptions in category 2 can apply to research involving children.

**Wards of the State**

The federal regulations providing special protections for children include additional limitations on some research involving children who are wards of the state or any other agency, institution, or entity. Where the research involves greater than minimal risk to the subjects with no prospect of direct benefit to individual subjects, the research must either be related to their status as wards, or else be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. The IRB will require, for each child who is a ward, appointment of an advocate in addition to any other individual acting on behalf of the child as a guardian or in loco parentis.

The IRB will be particularly concerned with the involvement of HIV-infected children who are in foster care, but who are also not wards. Many of these children are from racial or ethnic minorities. The IRB will give special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially be of benefit to them.

Finally, whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included as participants simply because of their availability to the investigator.

## RESEARCH INVOLVING PRISONERS

Inasmuch as prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, DHHS regulations at 45 CFR 46, subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners as subjects.

The provisions of subpart C apply to any research conducted or supported by Midwest Division in which prisoners are subjects. This includes research that involves individuals who are prisoners at the time of enrollment in the research or individuals who become prisoners after they become enrolled in the research. In the latter situation, it is unlikely that review of the research and the consent document contemplated the constraints imposed by incarceration.

"Prisoner" is defined by HHS regulations at 45 CFR part 46.303(c) as "any individual involuntarily confined or detained in a penal institution. The term is intended to encompass 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."

When the IRB reviews a protocol involving prisoners as subjects, the composition of the IRB will satisfy the following requirements of HHS regulations at 45 CFR 46.304(a) and (b):

- A majority of the IRB (exclusive of prisoner members) will have no association with the prison(s) involved, apart from their membership on the IRB.

- At least one member of the IRB will be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

Midwest Division's IRB has at least one prisoner representative who has a close working knowledge, understanding, and appreciation of prison conditions from the perspective of the prisoner. The prisoner representative is present at every IRB meeting, in which a protocol involving prisoners as subjects is reviewed, for all types of review of the protocol (including initial review, continuing review, review of protocol amendments, and review of reports of unanticipated problems involving risks to subjects). The curriculum vitae of the prisoner representative, serving on the IRB is on file in the IRB office and with OHRP.

**Permitted Research Involving Prisoners**

The categories of permissible research involving prisoners are the following:

*[Note that the definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk for other research, contained in 45 CFR 46, subpart A, 45 CFR 46.102(i). Minimal risk for prisoners, "is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.**"**]

(1) 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;

(2) 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;

(3) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research ; or

(4) Research on practices, both innovative and accepted, which have the intent and reasonable probability

of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.

**IRB Review of Research Involving Prisoners**

When the IRB is reviewing a protocol in which a prisoner is a subject, the IRB will make, in addition to other requirements under 45 CFR 46, subpart A, seven additional findings under 45 CFR 46.305(a), as follows:

(1) The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2) [noted above];

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

(3) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;

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

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

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

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

These seven additional findings made by the IRB will be documented in the minutes of the IRB meeting, in which the protocol was reviewed as a prison study.

**Approval of Research Involving Prisoners**

For research conducted or supported by Midwest Division to involve prisoners, two actions must occur:

(1) Midwest Division must certify to the Secretary (through OHRP) that the IRB has reviewed and approved the research under 45 CFR 46.305; and
(2) The Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

After a protocol involving prisoners as subjects has been approved by the IRB, the IRB Administrator will send

a certification letter that the IRB has made the seven additional findings required under 45 CFR 46.305(a), along with a copy of the research protocol, informed consent document, Application for Study Review, and Application for Research Involving Prisoners to OHRP.

*Research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to Midwest Division on behalf of the Secretary under 45 CFR 46.306(a)(2).*

Following receipt of the research proposal, OHRP will determine which, if any, of the four categories of research permissible under HHS regulations at 45 CFR 46.306(a)(2) the proposed research meets. OHRP will consult with appropriate experts with respect to certain research that falls under categories (3) and (4), as noted above. When applicable, OHRP also will publish in the Federal Register a notice of intent to approve such research. OHRP will issue its approval or lack thereof in writing to the institution on behalf of the Secretary under 45 CFR 46.306(a)(2).

Once an approval letter is received from OHRP in the IRB office, a copy of the letter and a non-contingent approval letter from the IRB will be forwarded to the investigator. At this point, and this point only, may an investigator begin to recruit prisoners as subjects.

**Frequently Asked Questions**

(1) *Does subpart C apply only where the research targets prisoners as subjects?*
Answer: No, subpart C applies whenever any human subject in a research protocol becomes a prisoner at any time during the study.

(2) *What should an investigator do if a subject becomes a prisoner after enrollment in research?*
Answer: The investigator should report this situation to the IRB immediately.

(3) *What should be done when a subject becomes a prisoner after enrollment in a study, which was not reviewed and approved by the IRB in accordance with the requirements of subpart C?*
Answer: When a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by IRB in accordance with the requirements of HHS regulations at 45 CFR part 46, subpart C, the principal investigator should promptly notify the IRB of this event. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.

NOTE: OHRP has allowed one important exception. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB will promptly re-review the protocol in accordance with the requirements of subpart C if the principal investigator wishes to have the prisoner subject continue to participate in the research.

(4) *Is an adolescent (e.g., age 14) detained in a juvenile detention facility a prisoner?*
Answer: Yes. In addition to subpart C, most likely subpart D would also apply.

(5) *Can research involving prisoners be expedited?*
Answer: Yes, however, OHRP recommends that the convened IRB review research involving prisoners as human subjects. At Midwest Division only continuing review of research involving prisoners under the following conditions may be reviewed via an expedited review procedure:

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

(6) *Do the exemptions apply to research involving prisoners?*
Answer: The exemptions [at 45 CFR 46.101(b)] do not apply to research involving prisoners.

(7) *What is the definition of minimal risk for prisoner research?*
Answer: For research involving prisoners, the definition of minimal risk requires reference to physical or psychological harm, as opposed to harm or discomfort, to risks normally encountered in the daily lives, or routine medical, dental or psychological examination of healthy persons.

"Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons."

## RESEARCH INVOLVING PREGNANT WOMEN, HUMAN FETUSES, AND NEONATES

DHHS regulations at 45 CFR 46, subpart B provide additional protections pertaining to biomedical and behavioral research involving pregnant women, human fetuses, and neonates as subjects.

Midwest Division's IRB will review research covered by this subpart and approve only research, which satisfies the conditions of all applicable sections of this subpart.

**Research involving pregnant women or fetuses (45 CFR 46.204)**

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
(2) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
(3) Any risk is the least possible for achieving the objectives of the research;
(4) If the research holds out
    a. The prospect of direct benefit to the pregnant woman,
    b. The prospect of a direct benefit both to the pregnant woman and the fetus, or
    c. No prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means,

    and the woman's consent is obtained;
(5) If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
(6) Each individual providing consent under (4) and (5) is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
(7) For children who are pregnant, assent and permission are obtained in accord with subpart D for studies involving children;
(8) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
(9) Individuals engaged in the research will have no part in any decisions as to the timing, method, or

procedures used to terminate a pregnancy; and

(10) Individuals engaged in the research will have no part in determining the viability of a neonate.

**Research involving neonates (45 CFR 46.205)**

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

(1) Where scientifically appropriate, pre-clinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
(2) Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
(3) Individuals engaged in the research will have no part in determining the viability of a neonate.
(4) The following requirements have been met as applicable:

a. Neonates of uncertain viability: Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:
   1. The IRB determines that:
      i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
      ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
   2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

b. Nonviable neonates: After delivery a nonviable neonate may not be involved in research unless all of the following additional conditions are met:
   1. Vital functions of the neonate will not be artificially maintained;
   2. The research will not terminate the heartbeat or respiration of the neonate;
   3. There will be no added risk to the neonate resulting from the research;
   4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
   5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A, except that the waiver and alteration provisions do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements.

c. Viable neonates: A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D (Additional Protections for Children Involved as Subjects in Research).

**Research involving, after delivery, the placenta, the dead fetus or fetal material (45 CFR 46.206)**

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities. For more information please contact the IRB office.

If information associated with the above mentioned material is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts are applicable.

**Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates (45 CFR 46.207).**

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 only if:

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

(2) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

a. That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or

b. The following:

1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
2. The research will be conducted in accord with sound ethical principles; and
3. Informed consent will be obtained in accord with the informed consent provisions of subpart A (Common Rule) and other applicable subparts.

## SUBJECTS IN "TREATMENT IND" STUDIES

Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications, which have not been proven either safe or effective, in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risks involved. The IRB must ensure that potential subjects are fully aware of the risks involved in participation.

The IRB should also pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. The question here is one of equitable selection and the involvement in research of vulnerable populations, particularly economically disadvantaged persons [21 CFR 56.111(a)(3)]. If subjects will be charged for use of the investigational drug or device, economically disadvantaged persons would likely be excluded from participation. The stated purpose of the Treatment IND exemption is to facilitate the availability of promising new drugs to desperately ill patients while obtaining additional data on the drug's safety and effectiveness. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to investigational drug or devices. The IRB will need to balance this interest against the possibility that unless the Sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA.

## COGNITIVELY IMPAIRED SUBJECTS

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a reassessment of decision-making capacity.

## AIDS RELATED RESEARCH

There are three ethical considerations that must be observed in the conduct of AIDS related research.

(1) THERE MUST BE FAIRNESS IN THE DISTRIBUTION OF BOTH RISKS AND BENEFITS OF RESEARCH: Caution is needed to make sure that age, competence, experience, education, position, life style, etc., are not used to determine eligibility for entrance into a study unless these factors are necessary for the research design.

(2) POSSIBLE BENEFITS OF THE RESEARCH MUST BE MAXIMIZED AND POSSIBLE HARMS MINIMIZED: As the research develops these matters will have to be reviewed from time to time to clarify what benefits may accrue to society as a whole, what benefits may accrue to subjects, and what possible harms may come to subjects. Special care must be taken to establish safeguards to prevent accidental or careless disclosure of confidential information. Improper disclosure could threaten family relationships, job security, employability or ability to obtain credit or insurance. Therefore, staff persons must be trained to handle information and data with due regard for the rights of subjects.

(3) THE RIGHTS OF RESEARCH SUBJECTS TO MAKE CHOICES BASED ON INFORMED JUDGMENTS MUST BE RESPECTED: These rights must be protected through a consent procedure which:

   a. Is legally effective;
   b. Is obtained in non-coercive circumstances with sufficient time and opportunity for subjects to make an informed decision;
   c. Does not attempt to waive the rights of subjects, or contain exculpatory language which is intended to limit the legal liability of the institution; and
   d. Is presented to subjects in language that is understandable to them--if necessary in language other than English.

Because of the special sensitivity of AIDS research, the IRB will exercise particular care in observing <u>all</u> applicable regulatory provisions. The IRB will see that risks to subjects are minimized consistent with sound research design, and that risks to subjects are reasonable in relation to benefits and the importance of the knowledge that may reasonably be expected to gain. Whenever appropriate, procedures already being performed on subjects for diagnostic or treatment purposes should be used. To ensure adequate review of AIDS studies, the IRB may consult with persons who have special expertise and with persons who are qualified to represent the interests of the subject population.

Perhaps the most sensitive aspect of AIDS research from the perspective of the rights and welfare of the subjects is the matter of confidentiality. 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.

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.

Investigators should consider and establish procedures for information disclosure in emergency situations involving the health either of research subjects or others. Whether and how to notify subjects, and/or physicians of findings about a subject should also be addressed.

Subjects are to be informed if tests confirm the presence of HTLV-III antibodies in their blood. Careful attention is to be given to the methods employed to inform subjects of positive findings. Persons providing this information should be qualified to impart sensitive information, alert to privacy and confidentiality issues, and prepared to provide subjects with references for additional counseling.

## INTERNATIONAL RESEARCH

All Midwest Division research performed outside of the United States (50 states and the U.S. territories) will be subject to the following Midwest Division policy, to ensure the protection of human subjects in international research studies and to comply with OHRP directives [August 27, 1998, updated July 21, 2000] requiring local context review of such studies.

### Policy

Protocol review and approval is required by:

(1) The outside country's IRB, Ethical Review Committee, or equivalent organization, and
(2) Midwest Division's IRB.

If foreign collaborators do not have their own IRB or comparable review committee, they may designate another IRB willing to review the research as the IRB of record. That IRB could be Midwest Division's IRB or another IRB in the host country.

If foreign collaborators do have their own IRB or comparable review committee, the Midwest Division investigator must ensure that the host country's IRB has had current education and training in Fundamental Human Research Protections and that it has procedures in place to ensure that subjects will be protected in a manner commensurate with the Common Rule. These procedures must be described in an agreement called an "assurance of compliance" with OHRP.

The federal regulations acknowledge that local customs, norms, and laws where the research will take place may differ from the Common Rule and provide options for listing different standards in foreign assurances of compliance. Optional standards include, among others, the Canadian Tri-Council Policy, the Indian Council of Medical Research, and the CIOMS International Ethical Guidelines (biomedical).

### Midwest Division IRB Review

All of the Midwest Division IRB policies for research studies conducted within the United States apply to international research. In addition international research protocols should include:

(1) Explanations of cultural differences that influenced the study design and the consent process;
(2) Rationale for conducting the study with an international population;
(3) Information regarding the host country's IRB, Ethical Review Committee or equivalent organization and documentation of its approval of the research, if applicable (The Midwest Division IRB may require meeting minutes from the committee in the host country);
(4) A copy of the letter(s) of agreement on letterhead stationary with signatures from the local host institution(s), and from government officials (as necessary) to cooperate in the proposed research;
(5) A copy of the consent form (if used) in English, a copy in the appropriate native language(s), and a copy

of the "back translation";

(6) Information regarding the literacy level of the expected subjects and how this may affect the informed consent process;
(7) Information regarding why women were or were not included in the study;
(8) A description of the informed consent process including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects;
(9) A description of the processes for assuring anonymity and/or confidentiality of all data, and a description of the methods of transport and security of data to the United States, if applicable;
(10) If data will be collected by someone other than the researcher, the curriculum vitae of the individual and letters of agreement, should be included on letterhead stationary and with signatures from the research institutions;
(11) If compensation is given to subjects, justification for the amount of money or goods should be provided and an explanation as to how this compensation is proportionate to the average annual income of people in the host country.

It is the practice of the Midwest Division IRB to give full board review to all research studies conducted outside the United States that include human subject contact. For studies that involve no contact with subjects and that are minimal risk (e.g., chart reviews or additional laboratory analysis of previously collected samples), expedited review of the study may be granted by the Midwest Division IRB. If a minimal risk study receives expedited review, a consultant familiar with the local context will be asked to provide to the reviewer with a written evaluation for local context review.

**Special IRB Considerations:**

<u>For studies involving populations that have no written language:</u>

- Use an English consent form as a template for translation into the oral language
- The consent form should be signed by the interpreter, the study Principal Investigator, and the subject, who will be requested to make a mark or thumb print, as appropriate.
- Include a statement about the process of informed consent.

<u>For studies involving populations that utilize group consent:</u>

- Describe and justify the use of group consent.
- Provide a method to obtain private or individual subject assent, if possible.
- Provide a method of protecting those who choose not to participate in the study.

<u>For "non-therapeutic" research:</u>

- Provisions must be made for the study population to benefit from the research study.

<u>For "therapeutic" research:</u>

- Provisions must be made and documented to address the issue of why the study should or should not provide continued access to the experimental intervention (should it prove efficacious) or other research benefits, by the host after the completion of the study.

<u>For Federally funded studies:</u>

- A Federalwide Assurance is necessary to document that the international institution or performance site will conduct the research in accordance with United States Federal policies and regulations.

<u>For studies involving minors (participants under the age of 18 years):</u>

- The Midwest Division requirements for assent for minors in research studies are applicable.
- Written, parental permission is also required. If local customs and regulations are such that active parental permission would be culturally inappropriate, the researcher must supply the IRB with proof that such permission is not culturally appropriate. Examples of such proof would be specific regulations

(in English and certified to be accurate) that indicate that such permission is not required, an official letter from a ranking official in the country of interest indicating that such permission is not culturally appropriate, or the appearance at an Midwest Division IRB meeting by someone of official standing in the research or academic community who can attest to the cultural inappropriateness of the requirement for active parental permission.

- In those cases where seeking active parental permission for minors to participate in research is culturally inappropriate, a waiver of such permission may be granted at the discretion of the Midwest Division IRB, as long as the research does not place the participant(s) at untoward risk. Regardless of the type of risk, the participant(s) in the research retain(s) the right to discontinue participation, without penalty, at any time.
- If a waiver of active parental permission is granted, and if a letter informing the parents of the research is deemed appropriate, it must be written at a literacy level that would be understood by the parents, and should be sent to them by the most expeditious method possible. Midwest Division's IRB will review the "back translation" of this letter.

**Local Context Consultant**

The key requirement for local context review is that a person who is familiar with the customs and culture of the study population participates in the review at the Midwest Division IRB meeting. Consultants must be native to the country, have had knowledge of such customs and culture that was obtained through extended, direct experience in the community, or be a professional familiar with the local environment. The consultant will attend, in person or via telephone, convened Midwest Division IRB meetings as an *ad hoc* non-voting member of the Midwest Division IRB. Information on the protocol will be sent to the local context consultant at least one week in advance of the convened meeting. The review and recommendations of the consultant will be documented in the Midwest Division IRB minutes.

The Chair of the Midwest Division IRB or, if designated by the Chair, the IRB Administrator, will interview potential consultants and inform them of the responsibilities of local context consultants.

**IRB Continuing Review of International Research Studies**

A protocol will have only one local context review unless there are significant changes in the protocol or the risks to the subjects. Midwest Division's standard continuing review requirements will apply to international research studies.

## RESEARCH INVOLVING MEDICAL DEVICES

Except for certain low risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a premarket notification to FDA. FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendments device"). If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. The pre-market notification requirement for new devices and devices that are significant modifications of already marketed devices is set forth in section 510(k) of the Act. Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices". If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

**Investigational Device Exemption (IDE)**

Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR 812].

The following clinical investigations of devices may be exempt from the IDE regulations [21 CFR 812.2(c)].

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
(3) A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
(5) A device intended solely for veterinary use.
(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
(7) A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "non-significant risk" (NSR). The determination that a device presents a non-significant or significant risk is initially made by the sponsor. The proposed study is then submitted to FDA, for SR studies, or to the IRB, for NSR studies.

The sponsor/investigator should provide the IRB with the following information:

(1) A risk assessment,
(2) The rationale used in making the risk determination,
(3) A description of the device,
(4) Reports of prior investigations with the device,
(5) The proposed investigational plan,
(6) A description of patient selection criteria and monitoring procedures,
(7) Information regarding whether other IRBs have reviewed the proposed study and what determination was made, and
(8) FDA’s assessment of the device's risk if such an assessment has been made.

Midwest Division’s IRB will review the above-mentioned material, and make a final risk determination based on its own review. The IRB may also consult with FDA for its opinion.

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

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

If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to the IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin immediately, without submission of an IDE application to FDA. If the IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to the IRB as an NSR investigation.

**SR versus NSR**

An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; (2) is used in supporting or sustaining human life; (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; OR (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk."

The risk determination will be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB will consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. For example:

(1) The study of a pacemaker that is a modification of a commercially-available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker will only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.
(2) The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

The following examples are provided to assist sponsors and investigators in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

Examples of NONSIGNIFICANT RISK DEVICES: (1) Low Power Lasers for treatment of pain, (2) Caries Removal Solution, (3) Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions), (4) Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use, (5) Conventional Gastroenterology and Urology Endoscopes and/or Accessories, (6) Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular), (7) Conventional Implantable Vascular Access Devices (Ports), (8) Conventional Laparoscopes, Culdoscopes, and Hysteroscope, (9) Dental Filling Materials, Cushions or Pads made from traditional materials and designs, (10) Denture Repair Kits and Realigners, (11) Digital Mammography [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.], (12) Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities), (13) Externally Worn Monitors for Insulin Reactions, (14) Functional Electrical Neuromuscular Stimulators, (15) General Biliary Catheters General Urological Catheters (e.g., Foley and diagnostic catheters), (16) Jaundice Monitors for Infants, (17) Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters, (18) Manual Image Guided Surgery, (19) Menstrual Pads (Cotton or Rayon, only), (20) Menstrual Tampons (Cotton or Rayon, only), (21) Nonimplantable Electrical Incontinence Devices, (22) Nonimplantable Male Reproductive Aids with no components that enter the vagina, (23) Ob/Gyn Diagnostic Ultrasound within FDA approved parameters, (24) Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain, (25) Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings).

Examples of SIGNIFICANT RISK DEVICES:

(1) *General Medical Use*

Catheters:

*Urology - urologic with anti-infective coatings

*General Hospital - except for conventional long-term percutaneous/implanted/subcutaneous/intravascular

*Neurological - cerebrovascular, occlusion balloon

*Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system

Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications

Surgical Lasers for use in various medical specialties

Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology.

(2) *Anesthesiology***:** Breathing Gas Mixers, Bronchial Tubes, Electroanesthesia Apparatus, Epidural and Spinal Catheters, Epidural and Spinal Needles, Esophageal Obturators, Gas Machines for anesthesia or analgesia, High Frequency Jet Ventilators greater than 150 BPM, Rebreathing Devices, Respiratory Ventilators, Tracheal Tubes.

(3) *Cardiovascular:* Aortic and Mitral Valvuplasty Catheters, Arterial Embolization Devices Cardiac Assist Devices [artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices], Cardiac Bypass Devices [oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices], Cardiac Pacemaker/Pulse Generators [antitachycardia, esophageal, external transcutaneous, implantable], Cardiopulmonary Resuscitation (CPR) Devices, Cardiovascular/Intravascular Filters, Coronary Artery Retroperfusion Systems, Coronary Occluders for ductus arteriosus/atrial/septal defects, Coronary and Peripheral Arthrectomy Devices, Extracorporeal Membrane Oxygenators (ECMO), Implantable Cardioverters/Defibrillators, Laser Coronary and Peripheral Angioplasty Devices, Myoplasty Laser Catheters, Organ Storage/Transport Units, Pacing Leads, Percutaneous Conduction Tissue Ablation Electrodes, Peripheral/Coronary/Pulmonary/Renal/Vena Caval/Peripheral Stents, Replacement Heart Valves, RF Catheter, Ablation and Mapping Systems, Ultrasonic Angioplasty Catheters, Vascular and Arterial Graft Prostheses, Vascular Hemostasis Devices.

(4) *Dental*: Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications, Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA), Dental Lasers for hard tissue applications, Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants, Subperiosteal Implants, Temporomandibular Joint (TMJ) Prostheses.

(5) *Ear, Nose, and Throat*: Auditory Brainstem Implants, Cochlear Implants, Laryngeal Implants, Total Ossicular Prosthesis Replacements.

(6) *Gastroenterology and Urology:* Anastomosis Devices, Balloon Dilation Catheters for benign prostatic hyperplasia (BPH), Biliary Stents, Components of Water Treatment Systems for Hemodialysis, Dialysis Delivery Systems, Electrical Stimulation Devices for sperm collection, Embolization Devices for general urological use, Extracorporeal Circulation Systems, Extracorporeal Hyperthermia Systems, Extracorporeal Photopheresis Systems, Femoral/Jugular/Subclavian Catheters, Hemodialyzers, Hemofilters, Implantable Electrical Urinary Incontinence Systems, Implantable Penile Prostheses, Injectable Bulking Agents for incontinence, Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic), Mechanical/Hydraulic Urinary Incontinence Devices, Penetrating External Penile Rigidity Devices with components that enter the vagina, Peritoneal Dialysis Devices, Peritoneal Shunt, Plasmapheresis Systems, Prostatic Hyperthermia Devices, Urethral Occlusion Devices, Urethral Sphincter Prostheses, Urological Stents (e.g., ureteral, prostatG).

(7) *General and Plastic Surgery:* Absorbable Adhesion Barrier Devices, Absorbable Hemostatic Agents, Artificial Skin and Interactive Wound and Burn Dressings, Injectable Collagen, Implantable Craniofacial Prostheses, Repeat Access Devices for surgical procedures, Sutures.

(8) *General Hospital*: Implantable Vascular Access Devices (Ports) - if new routes of administration or new design, Infusion Pumps (implantable and closed-loop - depending on the infused drug).

(9) *Neurological***:** Electroconvulsive Therapy (ECT) Devices, Hydrocephalus Shunts, Implanted Intracerebral/Subcortical Stimulators, Implanted Intracranial Pressure Monitors, Implanted Spinal Cord and Nerve Stimulators and Electrodes.

(10) *Obstetrics and Gynecology*: Antepartum Home Monitors for Non-Stress Tests, Antepartum Home Uterine Activity Monitors, Catheters for Chorionic Villus Sampling (CVS), Catheters Introduced into the Fallopian Tubes, Cervical Dilation Devices, Contraceptive Devices [Cervical Caps, Condoms (for men) made from new materials (e.g., polyurethane), Contraceptive *In Vitro* Diagnostics (IVDs), Diaphragms, Female Condoms, Intrauterine Devices (IUDs), New Electrosurgical Instruments for Tubal Coagulation, New Devices for Occlusion of the Vas Deferens, Sponges, Tubal Occlusion Devices (Bands or Clips)], Devices to Prevent Post-op Pelvic Adhesions, Embryoscopes and Devices intended for fetal surgery, Falloposcopes and Falloposcopic Delivery Systems, Intrapartum Fetal Monitors using new physiological markers, New Devices to Facilitate Assisted Vaginal Delivery, Thermal Systems for Endometrial Ablation.

(11) *Ophthalmics:* Class III Ophthalmic Lasers, Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use, Corneal Implants, Corneal Storage Media, Epikeratophakia Lenticules, Extended Wear Contact Lens, Eye Valve Implants (glaucoma implant), Intraocular Lenses (IOLs) [21 CFR part 813], Keratoprostheses Retinal Reattachment Systems [fluids, gases, perfluorocarbons, perfluorpropane, silicone oil, sulfur hexafluoride, tacks], Viscosurgical Fluids.

(12) *Orthopedics and Restorative***:** Bone Growth Stimulators, Calcium Tri-Phosphate Hydroxyapatite, Ceramics Collagen and Bone Morphogenic Protein Meniscus Replacements, Implantable Prostheses (ligament, tendon, hip, knee, finger), Computer Guided Robotic Surgery.

(13) *Radiology*: Boron Neutron Capture Therapy, Hyperthermia Systems and Applicators.

**IRB and Sponsor Responsibilities Following SR/NSR Determination**

If the IRB decides the study is Significant Risk:

(1) IRB Responsibilities:
   a. Notify sponsor and investigator of SR decision
   b. After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

(2) Sponsor Responsibilities:
   a. Submit IDE to FDA or, if electing not to proceed with study, notify FDA of the SR determination;
   b. Study may not begin until FDA approves IDE and IRB approves the study.
   c. Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

If the IRB decides the study is Nonsignificant Risk:

(1) IRB proceeds to review study applying requisite criteria [21 CFR 56.111]
(2) If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

**IRB Review of the Protocol and Informed Consent**

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

## RESEARCH INVOLVING INVESTIGATIONAL NEW DRUGS (IND)

An IND application must be filed when:

(1) A sponsor wishes to test a newly developed drug to see if its safety and efficacy are such that it can be approved for marketing,
(2) For studies of drugs that are already licensed if the intent of the study is to generate data that will lead to approval of a new advertising claim, a new clinical indication, or a new formulation of the product, and
(3) To add a new study design, a new patient group, or a new clinical indication to the evaluation of a product that is under study but not yet marketed.

If a drug is already licensed and approved by the FDA for marketing in the United States, it may be studied without an IND, as long as the study is not designed to change the approved indications, advertising claims, or labeling of the product. The study must not be one that changes dose, route of administration, or target population in a way that is likely to increase risk. The study is still subject to all of the usual requirements for IRB oversight, and the study must not violate any of the FDA's rules about advertising and promotion of drugs.

The overarching purposes of the IND process are to ensure the rights and welfare of study subjects and to ensure the quality and integrity of the data on which licensing applications are to be based. The former dominates the process in consideration of Phase I trials, whereas data quality questions become more important in later trials.

The process begins with the submission of a "Notice of claimed investigational exemption for a new drug: by the sponsor." This application sets forth the background information establishing that the time is right to move into human studies, and it sets forth a fair amount of detail about the plan of investigation in humans. A detailed protocol for the first human studies and a complete investigators' brochure for them are typically made part of the initial application. Specific content guidelines are provided at 21 CFR 312.23. The FDA then has 30 days to respond. FDA approval is for a very specific course of study, and is not a more general permission to study the drug. Once this approval has been secured, investigators should submit the study along with the necessary submission materials to the IRB.

The investigator and sponsor then have a number of recordkeeping and reporting obligations that must be satisfied. Data must be kept secure, and must be verifiable. Data must be monitored for safety issues as well as for study quality. Adverse events must be reported, both to the FDA and to the IRB. Changes in protocols must be submitted for approval, both to the FDA and to the IRB, and may not be implemented until approved by both, unless their purpose is to protect subjects from serious harm (for example, by removing a newly recognized substantive risk). Annual progress reports must be submitted to the FDA, as must continuing review applications/reports to the IRB.

A sponsor may withdraw an IND at any time, with or without cause. The FDA may also terminate an IND under a number of circumstances. A "clinical hold" is a suspension of an IND, during which no new subjects may be enrolled, and subjects who have already been enrolled may only continue the study drug if it is clinically necessary for them to do so. This action may be taken when it appears that subjects are being exposed to greater risk than had originally been recognized; the IND, and the study are then often reactivated when appropriate adjustments in study design have been made. A "clinical hold" may also result if the researchers' qualifications are called into serious question, or if the study design proves flawed in a way that precludes meaningful results.

More serious deficiencies may lead to termination of an IND. In that case, reactivation is not foreseen and the project is shut down. If the cause is clear and compelling danger to research subjects, this may be a rather precipitous action. If it is for problems in study conduct that do not place subjects at increased risk, the FDA will ordinarily notify the sponsor of the intent to terminate the IND and give the sponsor an opportunity to respond.

## RESEARCH INVOLVING INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS, AND MEDICAL DEVICES

"Investigational use" suggests the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a drug or device is to develop information about the product's safety or efficacy, submission of an IND or IDE is required.

However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(1) It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
(2) It is not intended to support a significant change in the advertising for the product;
(3) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(4) It is conducted in compliance with the requirements for IRB review and informed consent;
(5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
*(6)* It does not intend to invoke 21 CFR 50.24, *Exception from Informed Consent Requirements for Emergency Research.*

Midwest Division's IRB will review studies submitted with IND exemption requests to determine whether they meet the above exemption criteria. If the IRB determines that the exemption criteria are not met or the IRB is not certain whether the exemption criteria are met and an IND has not been obtained, it will ask the investigator to submit an IND or have the FDA make a determination on the requirement for an IND. If the FDA determines that an IND is not necessary, it will provide an exemption letter. A copy of this letter should be provided to the IRB. Should the FDA determine that an IND is required, a complete IND application must be submitted to the FDA for review. Upon completion of review, the FDA will send the investigator a letter. The IRB will withhold approval of the study until the investigator provides a copy of either the FDA determination letter or the IND number provided by the FDA.

IND application and approval/exemption is specific to the protocol rather than to the drug. Any proposed modifications to the protocol that significantly affect the safety of the subject or the scope of the investigation (e.g., a new protocol with the same drug) must be submitted to the FDA for review.

## GENETIC RESEARCH

Genetic research may require special considerations.

a. Type of Review: At first consideration, much genetic research may *appear* to meet the criteria for expedited review. These include:
   1. Pedigree studies, which look for a pattern of inheritance of a gene;
   2. Positional cloning studies, which are conducted to identify particular genes;
   3. Diagnostic studies, which gather samples to develop techniques to determine the presence of specific DNA mutations.

   However, these studies may create a vulnerable population in that subjects' autonomy may be compromised. Therefore the full IRB must review these studies to answer the following questions:
   1. Will the samples be made anonymous to maintain confidentiality? If not, to what extent will the results remain confidential; and who will have access to them?
   2. Will the samples be used for any additional studies not made explicit at the time of donation, or will the samples be destroyed after specified, one-time use?
   3. Will the donor be informed of any and all results obtained from his or her DNA? Will the donor be informed of the results of the entire study?
   4. Will family members be implicated in the studies without consent?

b. Privacy and Confidentiality Issues: Privacy and confidentiality issues are one of the most challenging regulatory aspects of genetic research. Because of the sensitive nature of the information that may be generated from genetic research studies, it is critical that investigators establish a method to secure information in a highly confidential manner. Studies that have the potential to ultimately predict the likelihood of subsequent serious illness could place participants at high risk for psychological and social harm. This type of sensitive information could adversely affect an individual's future insurability and employability as well as have significant impact on his or her psychological well being. Thus, IRB review must be scrupulous in assuring that privacy and confidentiality are always maintained.

   As genetic research may yield information of the most private nature, the IRB and potential research subject must understand exactly who will have access to study information and under what circumstances. This issue of disclosing research results to the subject should be explicitly addressed in the protocol and consent. Investigators and IRBs have to weigh the risks and benefits of giving a subject access to research results. Something that may be overlooked is the possibility that the disclosure of unanticipated or incidental information may harm the subject. An additional important consideration is the potential need for genetic counseling. It is impossible to clearly define the situations for which counseling is indicated, but IRBs should consider the potential benefits of genetic counseling to participants in these studies.

c. Use of Tissue or Cell Banks: Genetic studies often involve the use of tissue or cell banks that may involve the long-term storage of biological materials. Because the results of future studies may pose harm to individuals, it is crucial that participants be fully informed about their subsequent knowledge or research results. Whenever possible, genetic test results should be stored in a secure manner. During the informed consent process, it is critical that participants understand both the inherent risk of this type of research and, if it is the case, that they will not be informed of the results of subsequent studies performed on their tissue.

d. Subjects' Rights to Withdrawal: Ethical research requires that subjects have the right to withdraw from research participation at any point in the study. In genetic research, there is the potential for continuation of individual risk after withdrawal from the study when there is long-term storage of tissue. For this reason, it is important to determine if the research plan provides for the destruction of all stored data and tissue if the subject wants this to be done. If the research plan does not provide for tissue or data destruction, the study may still be ethical as long as participants understand this limitation.

e. IRB Review: A critical first step in the IRB review process of genetic studies is the determination of the predictive value of the study results. If there is reasonable scientific evidence that the expression of certain genetic markers within a study accurately predicts for a particular disease or condition, then participants are at risk, and the IRB must know the answers to a detailed list of questions before a determination can be made:

1. Are clear guidelines established for disclosure to participants of interim or inconclusive research results?
2. Will participants be informed of research results at each point in the research?
3. If information is discovered about the participant that may have implications for biologic family members, what are the plans to protect confidentiality?
4. Will limits on such protections be clearly communicated to participants, including obtaining advance consent to such disclosures (e.g., when family members will be warned about health risks)?
5. Will the possible psychological and social risks of genetic research be adequately considered in the consent process?
6. Will appropriate counseling be provided, both as part of the consent process and when communicating test or other research results to participants?
7. Will participants be informed about the possibility of important incidental findings such as paternity, disease, or conditions other than the one(s) that is/are the focus of the study?
8. Will the data be protected from disclosure to third parties, such as employers and insurance companies?
9. Will the participant be told about the potential consequences if a third party becomes aware of the study findings?
10. Will the data be stored in a secure manner?
11. Will the data be coded so as to protect the identity of the subjects?
12. Is a request for a certificate of confidentiality appropriate?
13. Does the PI plan to disclose research findings to subjects' physicians for clinical use? Are such plans appropriate?
14. Will the possibility of such disclosures be discussed in the consent process?
15. Will vulnerable populations be adequately protected?
16. Under what circumstances can a research participant give permission to involve a minor or an adult who lacks decision-making capacity in an aspect of this study?
17. What are the provisions for protecting the confidentiality of tissue samples?
18. What procedures will be used to get the subject's permission to store tissue or data for additional research in the future or for non-research medical practice?
19. What will happen to research data and tissue if a subject elects to withdraw from the study?
20. Are the implications of study withdrawal in terms of destruction or use of established data or tissue clearly explained in the consent document?
21. Do the plans to publish or present data from this study threaten the privacy or confidentiality of participants?

22. If the research may involve family members:
    a. Is the strategy for recruiting family members sensitive to privacy and confidentiality issues?
    b. Will information be obtained from the medical records of family members?
    c. If so, should consent be obtained from the family members to access this information?

Alternatively, if there is no clear evidence that a particular marker has predictive value, then there is virtually no risk to participants.

f. Informed Consent: The following information should be included in the consent document:
1. Clearly explain whether the subjects will have access to information obtained as part of this study. Explain what information they will be given whether they ask for it or not.
2. Explain if subjects may learn things about themselves or their family that they do not want to know, or that they may be uncomfortable knowing.
3. Explain if family members may learn about information generated in this study and the potential implications of this knowledge.
4. Explain if participation in this study may compromise the subjects' insurability.
5. Explain if participation in the study may prompt the subject to take actions that may incur unanticipated costs or expose the subject to additional risks. (i.e. genetic counseling may be expensive).
6. Accurately describe the limitations of protection of privacy and confidentiality.
7. Explain what it means to withdraw from this study in terms of the destruction or use of data or tissue related to the study.
8. Include an appropriately detailed explanation of all costs that are likely to be incurred by the subject or family members as a result of participation in the study. Address both the costs of procedures required by the study and costs, like genetic counseling, additional genetic testing, or psychological counseling, that the subject or family may be advised to pay based on study results.

g. Gene Therapy Research:
Gene therapy research (administration of recombinant vectors), which is carried out to develop treatments for genetic diseases at the DNA level, presents obvious and not so obvious questions, including – considerations of delivery methods, target population, and required follow-up. Such protocols will likely require use of external consultants to provide independent guidance to the IRB. If the project involves gene therapy to human subjects for other than clinical purposes, the study must be reviewed and approved by the National Institutes of Health Recombinant DNA Advisory Committee prior to IRB approval. Monitoring must be adequate, and a DSMB will be required. Because there is still little regulatory guidance and relatively few ethical precedents, genetic research will require close scrutiny, and the input of experts in this area.

## RESEARCH IN EMERGENCY SETTINGS (REVIEW OBTAINED PROSPECTIVELY)

1. The IRB, with the concurrence of a licensed physician who is either a member of the IRB or a consultant, and who is not participating in the research being reviewed, may waive the requirement for informed consent in certain emergency research ONLY if it finds and documents the following:

    (a) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

    (b) Obtaining informed consent is not feasible because:
        i. The subjects will not be able to give their informed consent as a result of their medical condition;
        ii. The intervention under investigation must be administered before consent from the subject's legally authorized representatives is feasible; and

iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(c) Participation in the research holds out the prospect of direct benefit to the subjects because:
i. Subjects are facing a life-threatening situation that necessitates intervention;
ii. Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(d) The clinical investigation could not practicably be carried out without the waiver.

(e) The proposed investigational or research plan:
i. Defines the length of the potential therapeutic window based on scientific evidence, and
ii. The Investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time, and
iii. If feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.

(f) The Investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

2. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.

3. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with applicable regulations.

4. Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(a) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(b) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(c) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(d) Establishment of an independent DSMB to exercise oversight of the clinical investigation; and

(e) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the Investigator has committed, if feasible, to attempting to contact, within the therapeutic window, the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The Investigator

will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

5. The study plan must ensure that, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member is informed of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document.

6. The study plan must ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

7. If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided above or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the Investigator and to the Sponsor of the clinical investigation.

## EMERGENCY USE OF INVESTIGATIONAL DRUGS OR DEVICES (REVIEW OBTAINED RETROSPECTIVELY)

1. An investigational drug or device may be used in an emergency prior to IRB review, provided that the patient is in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

2. Such emergency use must be reported to the IRB within 5 working days, and any subsequent use of the investigational drug or device is subject to prior review.

3. In such a situation, obtaining informed consent shall be considered feasible except in certain emergency situations where the Investigator has adequately documented the necessary exception under the guidelines described in 21 CFR 50.23. The Investigator must submit documentation to the IRB for review within 5 working days after emergency use of the investigational drug or device. In review of the documentation, the IRB will ensure that the Investigator and a physician not otherwise participating in the clinical investigation have adequately certified the following in writing prior to use of the investigational drug or device:

    (a) The human subject was confronted by a life-threatening situation necessitating the use of the investigational device or drug.

    (b) Informed consent could not be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

    (c) Time was not sufficient to obtain consent from the subject's legal representative.

    (d) There was no alternative method of approved or generally recognized therapy available that provided an equal or greater likelihood of saving the life of the subject.

4. If immediate use of the investigational drug or device is, in the Investigator's opinion, required to preserve the life of the subject, and time is not sufficient, prior to administering the investigational drug or device, to obtain an independent physician's opinion, the determinations of the Investigator must be reviewed in writing within 5 days after the use of the investigational drug or device by a physician not otherwise participating in the clinical investigation. In this event, a copy of the independent review must be submitted to the IRB within 7 working days after the use of the investigational drug or device.

5. Use of data generated prior to IRB approval: Whenever emergency care is initiated without prior review and approval, the patient may *not* be considered to be a research subject. HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval.

6. For DHHS-supported or conducted research, the physician may, without prior IRB approval, treat the patient/subject using a investigational drug or device (if the situation meets the FDA requirements), but the subject may not be considered a research subject and data derived from use of the investigational drug or device may not be used in the study.

## RESIDUAL BODY FLUIDS, TISSUES AND RECOGNIZABLE BODY PARTS

Body Fluids & Tissues: Research on existing specimens ("on the shelf" or frozen) without identifying information (e.g., no names, initials, hospital number, etc.) should be submitted to the IRB for review. Such research may be considered under expedited review, or may be exempted, but the application should be submitted for review and must include a short description of the research and where the tissue is coming from.

## PROTOCOLS LACKING DEFINITE PLANS FOR HUMAN INVOLVEMENT

1. Certain types of activities are planned and written with the knowledge that human subjects may be involved, but without definite plans for such involvement. Examples of such proposed activities are:

   (a) Training programs in which individual training projects remain to be selected or designed.

   (b) Research, pilot or developmental studies in which the involvement of human subjects depends on such things as the completion of survey instruments or prior animal studies.

2. The IRB can give "General Approval" to programs like those mentioned above with the understanding that the specific research protocol will be submitted to them once it has been developed. "General Approval" is not appropriate for individual projects or to meet grant deadlines.

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## IRB REVIEW THROUGHOUT THE STUDY'S IRB APPROVAL PERIOD

Investigators have a continuing responsibility to inform the IRB of:

(1) All modifications or addenda to the protocol or consent form,
(2) Adverse Events,
(3) Any circumstances or new information, which might change the perception of a favorable risk/benefit ratio, and
(4) Protocol Deviations.

## AMENDMENTS/ADDENDA TO APPROVED PROTOCOLS

It is the responsibility of the investigator to submit all amendments and addenda to approved protocols for review and approval by the IRB before implementation.

Amendments/addenda require review through one of the following mechanisms:

(1) Expedited Review of Amendments/Addenda: Amendments, which represent minimal risk changes to a project may receive expedited review by the IRB Chair (for a list of minimal risk changes, refer to the section on 'Expedited Reviews'). If the Chair determines that the change represents a minimal risk revision, approval may be granted. If, however, the Chair determines that the amendment/addendum does not qualify for an expedited review, the amendment request will be presented to the full Board for review and comments.

(2) Full IRB Review of Amendments/Addenda: Amendments and/or addenda that do not qualify for expedited review will be decided at a convened meeting of the full IRB. Such changes include, but are not limited to the following:

   a. Proposals to add an investigational new drug or device to an already approved study,
   b. Changes that are perceived to significantly affect the risk/benefit ratio for subjects,
   c. Changes made as a result of significant or unexpected toxicity in subjects,
   d. Principal investigator changes
   e. Significant revision of eligibility criteria, to include or exclude study participants,
   f. Introduction of a new procedure or instrument,
   g. Revision of the consent process,
   h. Addition of a new subject population,
   i. Changes in the duration of subject participation period, and
   j. Addition of procedures to audiotape and/or videotape subjects.

During a review of amendments/addenda, the IRB will address the following:

(1) Is this a minor amendment/addendum to the protocol or informed consent document?
(2) Does the investigator's rationale for the amendment/addendum make sense?
(3) Is this proposal the result of an adverse event?
(4) Does this amendment/addendum alter, in any way, the assessment of potential risks as described in the originally approved protocol?
(5) If "yes," is this additional risk justified?
(6) Are there potential benefits of this proposal?
(7) If "yes," do these potential benefits outweigh the potential risks?
(8) Does the amendment/addendum require the investigator to submit a revised protocol?
(9) Does the amendment/addendum require the investigator to submit a revised consent form?
(10) Does the amendment/addendum change the overall risk level for this study?
(11) How often should this study be reviewed by the IRB?

If the IRB approves the amendment/addendum, it will not change the approval/renewal date of a project. If the amendment/addendum changes the risk/benefit ratio, the IRB may require the study to be reviewed more frequently.

If the IRB does not approve the amendment/addenda, it will either recommend changes for the investigator to consider, or recommend that the investigator utilize the previously approved protocol, as is; either way, this will not change the approval/renewal date of the project. Detailed information regarding the review and further requirements will be provided to the investigator in a formal letter, within ten days of the meeting date of the review.

**Emergency Protocol Changes**

Rarely, an investigator may have to make an immediate change in the protocol to protect the safety of research participants. In these instances, the investigator should take *immediate action* to safeguard the health of the participants. If it is not possible for the investigator to notify the IRB prior to an emergency action, the investigator must notify the IRB in writing within 24 hours of the change in protocol, the circumstances that required its immediate implementation, and a revised consent form, if necessary.

**Methods to Ensure Investigators Do Not Implement Protocol Changes Without Prior IRB Approval**

In order to ensure that investigators do not implement protocol changes without prior IRB approval, the IRB office will conduct random audits of research records, and training programs for investigators. In addition, specific directives will be included in approval letters to investigators.

## SERIOUS ADVERSE EVENTS (SAES)

If adverse consequences or unexpected side effects are encountered in the course of the study, or new information becomes available which could change the perception of a favorable risk/benefit ratio, the investigator is responsible for informing the IRB PROMPTLY. Based on this information, the IRB may need to reconsider its approval of the study, require modifications to the study, or revise the continuing review timetable.

Investigators must report SAEs to the IRB within 48 hours of discovery, and 24 hours for deaths. For studies that have been determined by the IRB to be greater than minimal risk, these reports should be filed regardless of whether the SAE appears to be study related or is anticipated. For minimal risk studies, investigators must report only SAEs that they believe are probably or definitely study-related. It is the IRB's responsibility (not the investigator's) to determine which studies are classified as minimal risk. Follow up reports and a final written report should be sent to the IRB as soon as the investigator receives additional information regarding the event.

Once SAEs are received in the IRB office, the IRB Administrator will forward them to the IRB Chairperson for immediate review. If the IRB Chairperson is a researcher on the study, they will be sent to the designated External Reviewer for the specific study. The IRB Chairperson/ External Reviewer will review the SAE using the Midwest Division SAE reviewer form, and may ask for additional information from the investigators, such as hospital records, death certificates, pathology or autopsy reports, or request that it be reviewed by another reviewer, if necessary. If external documents such as hospital discharge summaries are not received by the IRB office within 90 days of initial request, SAE reviewers shall complete their report based on available information. Should additional information later become available, the SAE may be re-opened for review. The reviewer will determine, to the best of his/her abilities, whether the SAE's relationship to the study is unknown, probably related, possibly related, unlikely related, or not related. S/he will also make recommendations to the IRB regarding if protocol or consent form changes are necessary; and if so, what they are.

The IRB Administrator will contact the investigator if the reviewer requires more information, or if s/he is requesting any protocol or consent form changes.

At each convened meeting, the IRB reviews all new SAE reports and the corresponding reviewer reports. If protocol or consent form changes have been recommended by either the investigator or the Reviewer, the IRB will make the decision to accept/reject these proposed changes or to require new ones. The IRB may require more frequent review to monitor the protocol. In rare instances it may become obvious to the Chair and the Board that a study carries an unacceptable, unanticipated risk, and the investigator may be asked voluntarily to suspend the study, if he or she has not already done so, pending its re-evaluation. If the problem is deemed of sufficient magnitude, the IRB will direct the IRB Office to promptly report the injury or unanticipated problem involving risks to subjects to the appropriate institutional officials, OHRP, and any other sponsoring Federal department or agency.

**SAEs Involving a Death, Life-Threatening Event, or Serious Breach of Human Participant Protections**

The IRB Administrator will immediately inform the IRB Chair, applicable facility Director of Quality and Risk of SAEs involving a death, life-threatening event, or serious breach of human participant protections. The IRB Chair may decide to call a special IRB meeting to review the SAE and determine whether to modify the protocol and/or the consent form, suspend the study, or take other appropriate action. The Institutional Official will contact the Chair of Midwest Division's Board of Governors and they will decide whether to notify all Board members prior to the next scheduled meeting.

The IRB is aware that behavioral research investigators are not always successful in obtaining participants' death certificates, as they are not legally entitled to them. However, investigators should attempt to obtain death certificates for participants at least three times. If the third request is denied for a behavioral study in which there is little to no chance that the death could be related, the IRB will administratively close the review of the SAE.

**Reporting Requirements to External Agencies**

In accordance with 45 CFR 46.103(a) and 46.103(b)(5), the IRB Administrator will ensure prompt reporting of the following to the IRB and Midwest Division's Quality Director:

(1) Any unanticipated problems involving risks to participants or others,
(2) Any serious or continuing noncompliance with the Federal regulations (45 CFR 46) for the protection of human subjects, or the requirements, and determinations of the IRB, and
(3) Any suspension or termination of IRB approval

The Institutional Official will report the three aforementioned events and all deaths that have been determined to be possibly, probably, or definitely study related (categories 3, 4, and 5) to Midwest Division's Board of Governors, the OHRP, and the FDA (if appropriate).

**Additional Adverse Event Reporting Requirements**

Investigators are also responsible for reporting the following to the IRB in a timely fashion.

(1) New information that may impact the risk/benefit ratio of a study: This may include research findings from other studies, new information in the literature, new FDA labeling and alerts (www.fda.gov/cder), etc. After careful review, the IRB may recommend that the PI revise the consent form and/or protocol, or change the approval status of the study or the time-frame for continuing review.
(2) Irregularities in conducting the study: Examples include study enrollment prior to obtaining informed consent, improper recruitment (e.g., through coercion), protocol changes implemented without IRB approval, administering a study medication prior to obtaining written consent, administering incorrect dosage of study medication (regardless of injury), and the improper use of study equipment or devices (regardless of any injury).
(3) Data and Safety Monitoring Board reports: as soon as they are available
(4) Copies of all external SAEs: sent to the PI from the sponsor or other investigators for multi-site studies.

## PROTOCOL DEVIATIONS

The IRB will review the following:

(1) The deviation's net effect on risk,
(2) Why the deviation occurred,
(3) What is being done to prevent future occurrences,
(4) Whether participants were adversely affected by the deviation,
(5) Whether the participants were or should be informed of the deviation,
(6) Whether the deviation indicates additional risks for subjects,

(7) Whether it alter the risk/benefit ratio of the study, and
(8) Whether study or consent procedures be revised accordingly.

The IRB may note the occurrence of the deviation and the investigator's report of it, request more information, request protocol or consent form changes, or suspend enrollment or interaction with subjects if it believes that it is in the best interest of the subjects.

## SIGNIFICANT NEW FINDINGS

During the course of a study, the IRB may review reports generated from a DSMB, adverse event reports, current literature, and other sources to ascertain the status of the study and assess whether or not the risk/benefit balance is still acceptable. The IRB will review the information to determine whether or not new information needs to be conveyed to subjects, or if a segment of the population may be bearing an undue burden of research risk or being denied access to promising therapy.

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## IRB CONTINUING REVIEW

All protocols approved by the IRB are subject to continuing review, and must be reviewed at least once a year in order to be in compliance with federal human subjects regulations. Generally, at Midwest Division most 'minimal risk' studies are reviewed once a year, and most 'greater than minimal risk studies' are reviewed every six months. The study's risk level and review period will be noted in the original IRB approval letter.

The following factors are taken into consideration when determining the appropriate review interval, but are not limited to:

(1) Involvement of vulnerable populations;
(2) Research conducted internationally;
(3) Use of waiver of informed consent procedures, (e.g. surrogate consent);
(4) Research for which participants would be exposed to additional risks, e.g. breach of confidentiality, phase I studies, disproportionate number or severity of adverse events;
(5) Previous Administrative Holds or Suspensions of the research due to compliance, record-keeping or other concerns;

Although the IRB Administrator will send out reminder notices when continuing reviews are due, it is the ultimate responsibility of the investigator to submit progress reports to the IRB. Therefore, the investigator should not depend solely on IRB notification as a prompting for submitting all required information.

If a Progress Report is not submitted in time for the IRB to review and approve the protocol for the next period, at the end of the current approval period the protocol will be ADMINISTRATIVELY SUSPENDED. The continuation of research after expiration, or during suspension of IRB approval is a violation of federal regulations [45 CFR 46.103(a) and 21CFR 56.103(a)]. Once it has been administratively suspended, all research activity on this protocol must stop and no new subjects may be enrolled in the study. Only upon receipt of a formal letter to the IRB requesting reactivation and submission of a completed Progress Report will the renewal of approval process be continued. After approval is granted at a convened meeting of the IRB, the use of that protocol may be continued.

When a Progress Report is submitted for continuing review and the IRB determines that changes are necessary, there are two possible outcomes (if there is not sufficient time to return to the IRB with the requested information before the end of the current approval period):

(1) If the changes involve more than specific consent form issues: The investigator will be sent a NOTICE OF SUSPENSION effective on the expiration date of the prior approval until such time as the requested modifications have been reviewed and approved by the convened IRB.

(2) If only specific consent form changes are required: The investigator will be issued a letter indicating APPROVAL OF RENEWAL AS A FOLLOWUP STUDY. This letter grants approval of the continuation of the research described in the protocol for all currently-active subjects, but suspends the project to the accrual of new subjects until such time as the requested modifications to the consent form have been reviewed and approved by the Chairperson of the IRB.

In either case, the PRIOR APPROVAL REMAINS VALID until the expiration date originally indicated (only a vote of the full IRB can shorten or revoke prior approval), and the investigator has until that date to secure approval for the requested changes.

## EXPEDITED REVIEW FOR RENEWAL

A protocol (originally reviewed via expedited review) with no major changes and minimal risk classification may be eligible to receive continuing review on an expedited basis. Additionally, a protocol that had no accrual during the previous period, or which has not been awarded funding, or which remains open only to data analysis may be reviewed using an expedited review.

When conducting research under an expedited review procedure, the IRB Chairperson or designated IRB member conducts the review on behalf of the full IRB using the same criteria for renewal as stated in this policy. If the reviewer feels that there has been a change to the risks or benefits, he or she may refer the study to the full IRB for review.

## IRB CONTINUING REVIEW CONSIDERATIONS

Continuing review must be substantive and meaningful. In performing a continuing review, the IRB will look at an Application for Continuing Review, Progress Report, List of the Adverse Events over the past year, Previously Approved Protocol and Consent Form.

When considering whether or not to renew a study, the IRB revisits the same criteria used to grant initial approval. Therefore, it is the responsibility of the IRB to determine that:

(1) Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
(2) Selection of subjects continues to be equitable;
(3) Informed consent continues to be appropriately obtained and documented;
(4) Adequate provisions for monitoring the data collected to ensure the safety of the subjects is provided, when appropriate;
(6) Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, is provided, when appropriate; and
(7) Appropriate safeguards for vulnerable populations are provided.

Additionally, the IRB will address the following, during a continuing review:

(1) Are the number of subjects accrued consistent with the IRB approved number?
(2) Do the subject withdrawals indicate a problem with the protocol?
(3) Does the progress report include study amendments and new adverse event information?
(4) Are the risks and benefits as anticipated in the initial review?

(5) Have any subjects been seriously harmed?
(6) Has the IRB been informed of any unforeseen problems that may have occurred?
(7) Since the last review, is there new risk or benefit information that might affect subjects' willingness to participate in the research?
(8) Are there any new findings/knowledge/adverse event that should be reported to subjects?
(9) Does the progress of the research together with any new information indicate that the IRB should impose any new restrictions or relax any restrictions that were previously imposed?
(10) Does the consent form require revision?
(11) Are the procedures agreed upon at the beginning of the research still being used?
(12) Are the procedures for data monitoring adequate?
(13) If a study did not have a DSMB, should one be established?
(14) How often should this study be reviewed by the IRB?

## IRB CONTINUING REVIEW CONSIDERATIONS: CONSENT FORM

The purpose of this consent review is to continually improve the quality of the documents and to implement any changes newly required by the IRB.

When the IRB requests that routine changes be made to improve the quality of the consent document, it may only require that new subjects sign the revised consent document. However, in instances where the new consent document provides pertinent new information for all subjects, it may additionally require that current subjects (or only the ones who may be affected by the new information) be re-consented with the new document.

## DETERMINATIONS

Once the IRB has voted to approve a study, the IRB will again make a risk determination for the study, and then determine the review period.

On occasion, the IRB may also determine that the PI should submit a periodic report prior to the next continuing review due date. Examples of these types of reports include an update regarding recruitment, an update regarding a new procedure, an update after the first subject has been medicated, etc. These types of reports will be requested when the IRB feels that it is necessary to be updated on specific information within a certain time frame, however, it does not deem it necessary to conduct a complete continuing review at this time. When this type of periodic report is requested, it will be stated in the approval letter, along with the due date of the report.

The IRB will also determine the need for verification from outside sources.

If Subparts B, C, or D are applicable to the research, the IRB will once again review the research under the appropriate subpart and determine if the requirements have been satisfied.

## DETERMINATION OF THE CONTINUING REVIEW DATE

Several scenarios for determining the date of continuing review apply for protocols reviewed by the IRB at a convened meeting. To determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

- Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within 1 year of the date of the meeting, that is, by October 1, 2003.

- Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB chair or his/her designee can verify. On October 31, 2002, the IRB chair or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by October 1, 2003.

- Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2002, and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is, by October 29, 2003.

## EXTENSIONS OF APPROVAL PERIOD

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. Extensions beyond the expiration date will not be granted. If Continuing Review Report forms and other requested progress reports are not received as scheduled, the investigator must suspend the study and study enrollment until reports are reviewed and approved.

However, if the investigator is in communication with the IRB, the Continuing Review Report or other report is forthcoming, and in the opinion of the IRB, subjects participating in such a study would suffer a hardship if medical care were discontinued, appropriate medical care may continue beyond the expiration date for a reasonable amount of time. However, **new subjects cannot be enrolled**. The IRB will address on a case-by-case basis those rare instances where failure to enroll new subjects would seriously jeopardize the safety or well being of an individual. Prospective research data cannot be collected, and no procedures that are only being performed for the purposes of the protocol may be performed until a Continuing Review Report or other progress report is reviewed and approved.

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# SUBMISSION AND TERMINATION PROCEDURES

## NEW SUBMISSIONS

An investigator planning to conduct a new research project involving human subjects must submit the following:

(1) An Application for Behavioral Study Review or an Application for Bio-Medical Study Review,
(2) A detailed research protocol (federal grant application will suffice for this),
(3) Informed consent form(s),
(4) All surveys, questionnaires, etc. that are indicated in the protocol,
(5) Recruitment materials (e.g. flyers, advertisements, copy of radio advertisements),
(6) Data and Safety Monitoring Plan, or information regarding the Data and Safety Monitoring Board (if one has been established),
(7) Updated CV, and
(8) Certification of education in the protection of human subjects (if the IRB does not have this on file).

The following must also be submitted if applicable to the protocol:

(1) Supplemental Application for Research Involving Prisoners
(2) Supplemental Application for Research Involving Children
(3) Supplemental Application for Research Involving Pregnant Women, Human Fetuses, and Neonates
(4) Supplemental Application for Research Involving DNA, Tissue, Sample Banks

(5) Supplemental Application – Investigational Drug Information Record
(6) Supplemental Application – Indications for IND and IDE
(7) Financial Disclosure Form
(8) Statement of Investigator form (FDA 1572)
(9) Investigator's Brochure
(10) Grant Application
(11) If outside facilities or agencies are used as research sites, letters of agreement. If these facilities have an IRB, include a copy of the letter of approval for this study.
(12) Application for Expedited Review

The IRB Administrator reviews new applications for completeness. An incomplete application may be returned to the investigator. If there are questions regarding any portion of the application, investigators are strongly urged to discuss the issues with the IRB Administrator before submitting the final version of the application.

## THROUGHOUT THE STUDY'S IRB APPROVAL PERIOD

### Amendments/Addenda to Approved Protocols

The following should be submitted to the IRB office:
(1) An Application for a Protocol Amendment or Addendum,
(2) Revised Protocol,
- One version with track changes indicating where the protocol has been changed, and
- One clean version

(3) Revised Consent form, if necessary,
- One version with track changes indicating where the form has been changed, and
- One clean version

(4) Application for Expedited Review, if applicable.

### Serious Adverse Events

Investigators must report SAEs, using the SAE Report Form, to the IRB within 48 hours of discovery, and 24 hours for deaths. The SAE Form requires the investigators to make their best estimate, at the time of reporting, of the causal relationship between study participation and the SAE. The investigator should attempt to obtain records (which may include physicians' notes, hospital discharge summaries, biopsy, x-ray or other laboratory results, autopsy findings, etc.) to help clarify the nature of the SAE.

The descriptions below should be used to grade the SAE's study-relatedness:
(1) Not related:
Clearly due to extraneous causes (e.g., underlying disease, environment)
(2) Unlikely (must have 2):
a. Does not have a temporal relationship to intervention
b. Could readily have been produced by the participant's clinical state
c. Could have been due to environmental or other interventions
d. Does not follow a known pattern of response to intervention
e. Does not reappear or worsen with reintroduction of intervention
(3) Possibly (must have 2):
a. Has a reasonable temporal relationship to intervention
b. Could not readily have been produced by the participant's clinical state
c. Could not readily have been due to environmental or other interventions
d. Follows a known pattern of response to intervention
(4) Probably (must have 3):
3a, b, c, d above
e. Disappears or decreases with reduction in dose or cessation of intervention

(5) Definitely (must have all 5):
3a, b, c, d above
e. Disappears or decreases with reduction in dose or cessation of intervention and
f. Recurs with re-exposure

As noted on the SAE form, the investigator must also recommend to the IRB whether the SAE necessitates a change in the study protocol, and/or the consent form. The IRB will make the decision to accept/reject these proposed changes or to require new ones. Investigators should use their best judgment in terms of what would best protect and inform study participants.

Investigators are also responsible for reporting the following to the IRB in a timely fashion: new information that may impact the risk/benefit ratio of the study; irregularities in conducting the study, Data and Safety Monitoring Board reports, and copies of all external SAE reports.

### Protocol Deviations

It is the responsibility of the investigator to submit reports of all protocol deviations to the IRB after their occurrence. The following should be submitted to the IRB office:

(1) Deviation Form
(2) Revised Protocol, if necessary
- One version with track changes indicating where the protocol has been changed, and
- One clean version

(4) Revised Consent form, if necessary
- One version with track changes indicating where the form has been changed, and
- One clean version

(5) SAE Form, if necessary.

## PROGRESS REPORTS AND CONTINUING REVIEW REQUIREMENTS

For continuing reviews, the following should be submitted to the IRB office (three weeks in advance of the IRB meeting held prior to the study's expiration, and two weeks in advance of the study's expiration for an expedited review):

(1) Application for Continuing Review
(2) Progress Report
(3) Approved Protocol (if requesting revisions, one clean version and one with track changes)
(4) Approved Consent Form (if requesting revisions, one clean version and one with track changes)
(5) List of all AEs since the last review
(6) Protocol Summary
(7) Additional forms (when necessary) for protocol/consent form modification
(8) Application for Expedited Review (when applicable)

When changes in the protocol are to be made at the time of continuing review, the Continuing Review Form should be accompanied by an Application for a Protocol Amendment/Addendum, which details the proposed changes as well as an explanation of the rationale for the change, and an estimate of whether the change affects the risk/benefit ratio of the project. In addition to the form, submit a revised protocol, and one with track changes. If the changes require revision to the informed consent form, submit one clean version and one with track changes.

## SPECIAL REPORTING REQUIREMENTS

In special circumstances, determined at the time of review, the IRB may stipulate that some type of review should take place more frequently than once a year. When special reporting requirements are set as a condition of approval, the investigator must submit either the required information or a progress report, as indicated in the approval letter. For example, if the IRB is concerned with the recruitment rate of a study at the time of its continuing review, the IRB may stipulate in its approval that enrollment should be reviewed again in six months. Therefore, in six months the investigator must submit a letter to the IRB informing it of the study's current enrollment.

## FINAL REPORTS

When a project has been completed or when the investigator's participation in a project has ended, the investigator must submit a final report summarizing all activity carried out through the protocol.

For a Final Review, an investigator must submit the following to the IRB:

(1) Application for Final Review,
(2) Summary of Research Results, and
(3) Any publications resulting from the study.

## STUDY CLOSE-OUTS

If for any reason an investigator decides to close-out a study before its completion as per protocol, the investigator must submit a final report summarizing all activity carried out through the protocol, and the reasons for the study's closure.

To Close-Out a study, an investigator must submit the following to the IRB:

(1) Application for Final Review,
(2) Summary of all activity carried out through the protocol,
(3) Reasons for the study's closure, and
(4) A draft of a letter informing subjects' of the study's closure, if necessary.

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# CONFLICTS OF INTEREST

Clinical research and clinical trials pose special situations that require close scrutiny for several reasons. The IRB is responsible for ensuring that human subjects are fully informed and not placed at additional risk because of financial interests on the part of the investigator(s). In addition, Midwest Division is obligated to ensure that the results are free from a harmful conflict of interest (or any appearance thereof); otherwise, approval by the FDA may be jeopardized. Thus, Midwest Division will make every effort to ensure that conflicts of interest do not bias research conducted by investigators and do not put research participants at risk.

Additionally, no IRB member may participate in the initial or continuing review of any research project in which the member has a conflict of interest, except to provide information as requested. It is the responsibility of each member of the IRB to disclose any COI in a study submitted to the IRB, and recuse him or herself from deliberations and voting.

Investigators should disclose any conflict of interest to Midwest Division's Division Ethics and Compliance Officer. The Officer will send the IRB a report of his/her assessment of the real or perceived conflict of interest, along with a plan regarding any real conflict of interest.

Investigators should also disclose any conflict of interest to the IRB at the time of the initial application, its renewal, or whenever the status of the conflict changes. The IRB will review the investigator's disclosures and the conflict of interest officer's assessment of any real conflict of interest, taking particular note of the impact of the conflict on research integrity and risks to research participants.

The IRB will make the final decision about the conflict of interest and may require the following:

(1) Prohibition of the investigators' participation in the research
(2) Management of the conflict of interest through:
    a. Disclosure of the conflict to subjects in the consent form
    b. Public disclosure in articles and presentations
    c. Limiting the role of the Investigator
    d. External oversight of the study
    e. Investigator's deciding to sever relationships with the other organization.

### External Reporting Requirements

(1) FDA: The Food and Drug Administration (FDA) requires investigators to certify the absence of and/or disclose the existence of any financial conflict of interest.
(2) NIH: The National Institutes of Health (NIH) requires investigators to disclose any conflict of interest to the NIH Grants Management Officer at the NIH Institute funding the project.
(3) Other: Investigators should contact the sponsors of research in which they are participating to determine their requirements regarding conflicts of interest.

### Violations of COI Policy

If the IRB has reason to believe that an investigator has failed to disclose an actual or potential conflict of interest, it shall inform the Board of Govenors, who will inform the investigator of the basis for the belief and allow him/her an opportunity to explain.

If, after hearing the response of the investigator and pursuing further investigation, the Board of Govenors determines that the investigator has failed to disclose an actual or possible conflict of interest, it shall take appropriate disciplinary and corrective action.

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## EDUCATION REQUIREMENTS

OHRP strongly recommends that Institutions and the designated IRB establish educational training to ensure that research investigators, IRB members and staff, and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles, relevant Federal Regulations, OHRP guidance, other applicable guidance, state and local laws, and institutional policies for the protection of human subjects. Furthermore, OHRP recommends that a) IRB members and staff complete relevant educational training before reviewing human subject research; and b) research investigators complete appropriate institutional educational training before conducting human subject research.

Therefore, to satisfy this federal recommendation, and to provide the greatest protection to our research participants, Midwest Division encourages all investigators, research staff, and IRB members to complete training in human research protections, upon the submission of a new study for IRB consideration. This can be satisfied by successfully completing the Office of Human Protections (OHRP) online training, Human Research Protections at http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp

In addition to the OHRP program, Midwest Division may conduct educational presentations for IRB members, investigators, and research staff. We may offer such workshops as Ethical Decision Making, Fundamentals of Human Research Protection, Advanced Topics in Human Research Protection, HIPAA for Researchers, Responsible Conduct of Research, and Mock IRB Review, among others. A listing of the upcoming workshops is posted on Midwest Division's web site. Additionally, IRB staff members are often available to meet with investigators and their research staff to discuss IRB policies and procedures.

Investigators, Research Staff, and IRB Members are also encouraged to gain knowledge of the following:

(1) Principal Investigator's Procedure Manual for the Protection of Human Subjects in Research
(2) Midwest Division's IRB Policies and Standard Operating Procedures
(3) OHRP regulations regarding the protection of human subjects in research, 45 CFR 46.
(4) FDA regulations regarding the protection of human subjects in research, 21 CFR 50 and 56
(5) FDA regulations regarding investigational new drugs, 21 CFR 312
(6) FDA regulations regarding investigational device exemptions, 21 CFR 812
(7) Belmont Report
(8) Other State and Federal regulations and related material as applicable.

Materials relating to the above education program may be obtained in the IRB Office.

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## INVESTIGATOR NOTIFICATIONS

Initial submission: The investigator will be notified in writing of the IRB's decision as soon as possible after the meeting (within one week of the approval of the meeting minutes). For expedited reviews, investigators will receive written notification within three days of the review. If the approval is pending upon receipt and review of requested materials or responses from the investigator or Sponsor, the IRB must receive the response within 60 days of the date of notification; however, this period may be extended if the investigator/sponsor communicates a need for an extension.

Renewals and revisions: Investigators will be notified in writing as soon as possible as to action taken by the IRB for any continuing reviews or revisions (within one week of the approval of the meeting minutes). For expedited reviews, investigators will receive written notification within three days of the review.

Notification of approval: Investigators will be notified in writing of the approval (including the risk determination and period of approval) and provided with an IRB-approved version of the consent form. The IRB-approved consent form will be dated with the period of approval, and initialed by the Chairperson (or the IRB Administrator for the Chairperson). The Investigator will also be provided with a document entitled, "Principles to be Followed by Principal Investigators," which outlines the responsibilities of the investigator.

Disapproval: Correspondence will provide the reason(s) for disapproval and instructions to the investigator for appeal of this decision.

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## INVESTIGATOR APPEAL OF IRB ACTION

Investigators may appeal the revisions required by the IRB in the protocol and/or informed consent form. This appeal must be in writing and submitted to the IRB Administrator. Investigators may also appeal an IRB decision to disapprove a study. Any such appeal may be in writing or in person and must be reviewed by the full IRB at a convened meeting. If the appeal is denied and the study disapproved, the institution cannot override the IRB's decision.

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## SUSPENSION AND TERMINATION PROCEDURES

The IRB has the responsibility and authority to suspend or terminate approval of research that is not being conducted in accordance with IRB requirements or that has been associated with unexpected harm to subjects. A list of the reasons for any suspension or termination will be provided to the investigator, all appropriate governmental agencies, and Midwest Division's Institutional Official will be notified.

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## INCIDENTS OF NON-COMPLIANCE

Failure to report an adverse effect, or protocol deviation, or not submitting a Progress Report for renewal of approval in a timely fashion are breaches of the conditions under which IRB approval is granted, and could result in suspension of approval. Continuing, serious or multiple incidents of non-compliance may result in an IRB decision to monitor some or all protocols of a non-compliant investigator at more frequent time intervals. If non-compliance continues, the protocol(s) may be administratively terminated so that the research must end. The letter of Administrative Termination will be sent to the investigator, Institutional Official, OHRP, and any other sponsoring Federal department or agency. No new subjects may be recruited and all existing subjects in the study will be withdrawn from the study, as long as there are no safety issues. If follow-up of subjects for safety reasons is necessary, the subjects may continue on the study until such time that a safe alternative is found. The subjects should be informed of the termination of the protocol and any adverse events/outcomes should be reported to the IRB and the sponsor.

It should be understood that any use of human subjects without an approved protocol constitutes serious ethical misconduct. Moreover, should a subject be injured under such circumstances, the investigator may face significant legal exposure.

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## REPORTING REQUIREMENTS OF THE IRB OFFICE

The Prinicipal Investigator will report promptly to the IRB, appropriate institutional officials, OHRP, and any other sponsoring Federal department or agency:

(1) Any injuries to human subjects or other unanticipated problems involving risks to subjects or others,
(2) Any serious or continuing noncompliance with the regulations or requirements of the IRB, or
(3) Any suspension or termination of IRB approval for research due to continuing or serious noncompliance with the regulations or requirements of the IRB.

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## MAINTENANCE OF IRB RECORDS AND FILES

The IRB Office maintains the following IRB records:

(1) Current list of IRB membership and qualifications,

(2) Minutes of meetings, including information regarding member attendance, discussions held, decisions made and voting results, and

(3) All materials submitted to the IRB for initial and continuing review of each protocol/study including IRB applications, protocols, submitted and final informed consent forms, adverse reaction reports, protocol deviation reports, proposed protocol amendments/addendums, annual progress reports, copies of the Certificate of Confidentiality (if one is obtained), and all correspondence generated between the IRB, the investigator(s) and, where applicable, sponsoring agencies. This information is retained for a period of three years following the inactivation/termination of the project, regardless of study site.

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## IRB AUTHORIZATION AGREEMENTS

The IRB may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort as allowed and upon entering into an IRB Authorization Agreement as provided for by OHRP.

When Midwest Division's IRB determines that it will rely on another institution's IRB review of a study, or vice versa, Midwest Division's IRB Administrator will create an IRB Authorization Agreement. Midwest Division's Institutional Official, and the other institution's signatory official will sign the document, and copies will be kept on file at both institutions. The IRB Administrator will also amend the FWA accordingly, when appropriate.

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## COLLABORATING INDIVIDUAL INVESTIGATOR AGREEMENTS

The IRB may extend, for one or more research protocols, the applicability of its FWA to cover two types of collaborating individual investigators: collaborating independent investigators and collaborating institutional investigators.

OHRP notes that some human subjects research conducted by an assured institution may involve the following two types of collaborating individual investigators:

1. A collaborating independent investigator is:
   a. not otherwise an employee or agent of Midwest Division,
   b. conducting collaborative research activities outside the facilities of Midwest Division, and
   c. not acting as an employee of any institution with respect to his/her involvement in the research being conducted by Midwest Division.

2. A collaborating institutional investigator is:
   a. not otherwise an employee or agent of Midwest Division,
   b. conducting collaborative research activities outside the facilities of Midwest Division,
   c. acting as an employee or agent of a non-assured institution with respect to his/her involvement in the research being conducted by Midwest Division, and
   d. employed by, or acting as an agent of, a non-assured institution that does not routinely conduct human subjects research.

Midwest Division will extend its FWA to cover a collaborating independent or institutional investigator provided that all of the following conditions are satisfied:

(1) The principal investigator at Midwest Division directs and appropriately supervises all of the collaborative research activities to be performed by the collaborating individual investigator outside Midwest Division.

(2) The extension of the coverage of the FWA is put in place by use of an appropriate written agreement, such as the sample Individual Investigator Agreement, for each collaborating individual investigator who will be engaged in the research being conducted by the assured institution. Midwest Division will maintain the Individual Investigator Agreement, or other written agreement used by the assured institution, on file and provide copies to OHRP upon request.

(3) For collaborating institutional investigators, the appropriate authorities at the non-assured institution state in writing that the conduct of the research is permitted at their institution.

(4) Midwest Division and the responsible IRB designated under the FWA approve the extension of the assurance through either the Individual Investigator Agreement or other written agreement used by Midwest Division.

(5) The following documents are made available to the collaborating individual investigator: (a) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects or Research; (b) the HHS regulations for the protection of human subjects at 45 CFR part 46 and the FDA regulations at 21 CFR 50, 56, 312, and 812, when appropriate; (c) the FWA and applicable Terms of the FWA for the assured institution; and (d) the relevant institutional policies and procedures for the protection of human subjects of Midwest Division.

(6) The collaborating individual investigator understands and accepts the responsibility to comply with the standards and requirements stipulated in the documents referenced in the preceding paragraph and to protect the rights and welfare of human subjects involved in research conducted under the Individual Investigator Agreement or other written agreement used by Midwest Division.

(7) The collaborating individual investigator agrees to comply with all other applicable federal, international, state, and local laws, regulations, and policies that may provide additional protections for human subjects participating in research conducted under the Individual Investigator Agreement or other written agreement used by Midwest Division.

(8) The collaborating individual investigator agrees to abide by all determinations of Midwest Division's IRB and agrees to accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities conducted under the Individual Investigator Agreement or other written agreement used by Midwest Division.

(9) The collaborating individual investigator agrees to complete any educational training required by Midwest Division and/or the IRB prior to initiating research covered under the Individual Investigator Agreement or other written agreement used by Midwest Division.

(10) The collaborating individual investigator agrees not to enroll subjects in research under the Individual Investigator Agreement or other agreement used by the assured institution, prior to the research being reviewed and approved by the IRB.

(11) The collaborating individual investigator agrees to report promptly to the IRB/IEC any proposed changes in the research conducted under the Individual Investigator Agreement or other agreement used by Midwest Division. The collaborating institutional investigator agrees not to initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

(12) The collaborating individual investigator agrees to report immediately to the IRB any unanticipated problems involving risks to subjects or others in research covered under the Individual Investigator Agreement or other agreement used by Midwest Division.

(13) The collaborating individual investigator, when responsible for enrolling subjects, agrees to obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required under HHS regulations at 45 CFR part 46 and stipulated by the IRB.

(14) The collaborating individual investigator acknowledges and agrees to cooperate with the IRB's in its initial and continuing review, record keeping, reporting, and certification for the research covered by the

Individual Investigator Agreement, or other agreement used by Midwest Division. The collaborating institutional investigator agrees to provide all information requested by the IRB in a timely fashion.

When Midwest Division decides to extend, for one or more research protocols, the applicability of its FWA to cover collaborating individual investigators Midwest Division's IRB Administrator will create an Individual Investigator Agreement. Midwest Division's Institutional Official, and the individual investigator will sign the document, and copies will be kept on file at both institutions.