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CHAPTER 1

Purpose of this Handbook

The purpose of this Investigator's Handbook is to provide information and help to Sponsors, investigators, CRO's, SMO's and their staff as to their responsibilities while conducting a human research study overseen by Asentral, Inc. IRB.

The Asentral, Inc. Institutional Review Board (hereon referred simply as the IRB) is a committee(s) whose purpose is to ensure that the rights and welfare of human subjects are protected in all medical, behavioral and social sciences research. In accordance with federal and state regulations governing research, an IRB must review and approve research involving human subjects prior to its initiation. It is the responsibility of the IRB to determine whether proposed research exposes subjects to unreasonable or unnecessary risk, to review informed consent forms and process, and to monitor the progress of research. In its deliberations, the IRB will use the ethical principles as detailed in the Belmont Report (1979) to make its determination.

Before a research project involving human subjects is initiated, it must first be reviewed and approved by an IRB, and then conducted according to the procedures and guidelines set forth in the Federal and State regulations governing research and in accordance with the IRB's Standard Operating Policies and Procedures. This includes all research involving human subjects, including but not limited to drug studies, medical devices studies, and diagnostic studies (invasive or non-invasive), regardless from where the research is funded.

The IRB Chair or designee has the authority to act on behalf of the IRB when immediate action is required prior to a convened IRB meeting to protect the rights and welfare of human subjects. The IRB Chair or designee has the authority to evaluate and provide a resolution for emergent issues related to human subject protections that are not covered by these policies. Any such action will be brought to the attention of the convened IRB at the next meeting. The IRB also has the authority to promulgate or amend policies and procedures as necessary for the proper protection of human subjects in research.

Investigators bear the primary responsibility for ensuring that research protocols meet the standards established by both Federal and State regulation and the Institutional Review Board. Compliance with these regulations helps to ensure the protection of human subjects.

Federal Regulations referred to throughout this handbook are as follows:

45 CFR 46 (i.e. Title 45 Code of Federal Regulations Part 46: Protection of Human Subjects), hereafter referred to as the Common Rule, which applies to research involving human subjects conducted by the Department of Health and Human Services (DHHS) or supported in whole or in part by DHHS.

21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards), which apply to all research involving products regulated by the Food and Drug Administration (FDA), including research and marketing permits for drugs, biological products, or mechanical devices for human use, food and color additives, or electronic products.

It is the policy of the IRB that the same standards shall apply to all research, whether federally funded or not. When research involves products regulated by the FDA, both OHRP and FDA regulations apply, and the requirements of both sets of regulations must be met.

Introduction

Asentral Inc. is a commercial Institutional Review Board (IRB). It was incorporated in June of 2002 and began operations in November 2002. The IRB was founded by a group of research professionals as a commercial IRB with the distinction of providing immediate, personal, and professional service.

Asentral Inc., is a company answering the rapidly increasing demand for ethical review and oversight of clinical research in the community setting. Until recently such research was regarded as an adjunct to the 'real' research that occurred in the major academic and teaching hospital centers. Today, community based research has eclipsed institutions and hospitals in the progress of medical care with increasing participation by physicians who have chosen to practice in the community setting, with or without an academic affiliation. As with any research, there are unique, growing and ever-changing requirements, setting the stage for rigorous oversight. Asentral, Inc., an industry sponsored Institutional Review Board, provides such oversight.

The primary function of Asentral is to ensure that no research protocol participants are subjected to unwarranted risks. Recognizing that some risk is inevitable, our second function is to assure that it is minimized and that any volunteer patient is well informed about the risks. It is also necessary to ensure that potential benefits, either to the patient or society justify whatever risks may exist. We will also ensure that no volunteer is subjected to undue pressure to participate in any study. Asentral will determine that physicians undertaking research have the requisite credentials and expertise, and that all the data is gathered according to requirements of the research protocols and all applicable state and federal laws.

Mission

Our mission is to promote the continuation of sound clinical research by protecting the rights and well-being of clinical research subjects.

This mission statement includes the notion that not only is Asentral's goal to protect human subjects enrolled in clinical research trials, but also to be a participant in advancing sound clinical research without unnecessary delay, unnecessary costs or inefficiency.

Asentral, Inc. IRB Contact Information

The Asentral, Inc. IRB can be contacted at:

Address:	10 Mulliken Way Newburyport, MA, 01950
Phone:	978-462-6415
Fax:	978-462-6416
Web Address:	www.asentralirb.com
Hours:	8:30 AM – 4:30 PM EST
Email:	info@asentralirb.com

CHAPTER 2

IRB Authority

Asentral, Inc. IRB operates in compliance with the following:

- 45CFR 46 Protection of Human Subjects (DHHS)
- 21 CFR 50, 56, 312, 812 The FDA Regulations on Human Subjects Research
- ICH E6 International Conference on Harmonisation guidelines for Good Clinical Practice

In accordance with federal regulations, Asentral, Inc. IRB has the authority to approve, require modifications in (to secure approval), place restrictions upon, or disapprove human research activities of the research studies it oversees. It has the authority to suspend or terminate approval of research not being conducted in accordance with pertinent laws or IRB requirements; and to observe, or have a third party observe, the consent process and other aspects of the conduct of the research.

All human participant research under the oversight of Asentral, Inc. IRB is to be conducted in compliance with the principles of the Belmont Report and other ethical codes of the conduct for research, such as the Declaration of Helsinki and the Nuremberg Code, and is consistent with Good Clinical Practice (GCP) guidelines.

The IRB shall review all research documents and activities that bear directly on the rights and welfare of the subjects of proposed research, including all methods and materials that investigators propose to use to recruit human subjects.

CHAPTER 3

The Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research):

The following is taken from the OHRP IRB Guidebook.

It can be found at: http://www.hhs.gov/ohrp/archive/irb/irb_introduction.htm

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation

were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, **respect for persons, beneficence**, and **justice**, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

Respect for persons involves a 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.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles. The full text of the *Belmont Report*, which describes each of the three principles and its application, is provided in the Guidebook in Appendix 6; a summary follows.

Boundaries Between Practice and Research

While recognizing that the distinction between research and therapy is often blurred, *practice* is described as "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals." The Commission distinguishes *research* as designat[ing] an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. "The Report recognizes that "experimental" procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such "experimental" procedures should be investigated early, and that institutional oversight mechanisms, such as medical practice committees, can ensure that this need is met by requiring that "major innovation[s] be incorporated into a formal research project."

Applying the Ethical Principles

Respect for Persons. Required by the moral principle of respect for persons (*see* definition, above), **informed consent** contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether or not to participate, including the research procedure(s), their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Responding to the question of what constitutes adequate information, the Report suggests that a "reasonable volunteer" standard be used: "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some

direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. [*See* discussions on this issue in other sections of the Guidebook, including Chapter 6, "Special Classes of Subjects."] Each such class of persons should be considered on its own terms (*e.g.*, minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence. Closely related to the principle of beneficence (*see* definition, above), **risk/benefit assessments** "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the "validity of the presuppositions of the research;" (2) distinguish the "nature, probability and magnitude of risk...with as much clarity as possible;" and (3) "determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies."

Five basic principles or rules apply when making the risk/benefit assessment: (1) "brutal or inhumane treatment of human subjects is never morally justified;" (2) risks should be minimized, including the avoidance of using human subjects if at all possible; (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving "significant risk of serious impairment" (e.g., direct benefit to the subject or "manifest voluntariness of the participation"); (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice. The principle of justice mandates that the **selection of research subjects** must be the result of fair selection procedures and must also result in fair selection outcomes. The "justness" of subject

selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (*e.g.*, involving "undesirable" persons in risky research). Further, "social justice" indicates an "order of preference in the selection of classes of subjects (*e.g.*, adults before children) and that some classes of potential subjects (*e.g.*, the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that "arises from social, racial, sexual, and cultural biases institutionalized in society."

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are "easy to manipulate as a result of their illness or socioeconomic condition." Care should be taken to avoid overburdening institutionalized persons who "are already burdened in many ways by their infirmities and environments." Nontherapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate[s] to the specific conditions of the class involved."

What Activities are Considered Research?

In order to define what types of activities constitute research, it is generally accepted that any activity which includes a systematic design, using a scientific approach or protocol for the purpose of drawing conclusions, and which could add to generalizable knowledge in a particular area, constitutes research and must be reviewed and approved by an IRB if human subjects are involved. The Common Rule defines research as "[…] a systematic investigation including research development, testing and evaluation designed to develop or contribute to generalizable knowledge." The Belmont Report states: "[…] the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge…Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective." Certain activities which might not appear as research, such as quality assurance or improvement studies, may include or constitute research in a particular situation if there is a clear intent to contribute to generalizable knowledge.

Generally, whenever data is to be collected for evaluation, there is research activity involved. Whenever human subjects are involved, either directly or indirectly (e.g. chart reviews, use of pathological specimens, etc.), the research must be reviewed by an IRB. This is true even if there is no deviation from the standard of care which would otherwise be applied. The individuals from whom information is aggregated for analysis are considered human subjects, even if they receive no experimental treatment.

Researchers should employ sound study design in accordance with the standards of their discipline. Researchers should design studies in a manner that minimizes risks to participants.

The Asentral, Inc. IRB staff, in conjunction with the IRB Chairperson(s), determine whether the proposed activity is research involving human participants as defined in the preceding paragraph. The criteria for this determination will be an examination of a written summary of the proposed activity.

DEFINITIONS

Exempt Research refers to research meeting certain criteria [as outlined in 46 CFR 46.101(b)]. Research meeting this criteria is not subject to continuing review. The determination as to whether or not a project is exempt must be made by the staff of the IRB in conjunction with the IRB Chair or designee. The investigator does not have the authority to make this determination. The term exempt may be confusing because the project must in fact be submitted for review. Research being considered for exempt status are reviewed as they come in.

Expedited Review refers to a review procedure which takes place without a convened IRB, and may be used to review certain research activities which meet the criteria outlined in 45 CFR 46.110 and 21 CFR 56.110. Research being considered under expedited review are reviewed on an "as they are received" basis. If it is determined that a protocol cannot be expedited and requires full-board review, deadline dates would apply to the resubmission.

Human subject means an individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. Intervention includes physical procedures and manipulations of the subject or the subject's environment for research purposes.

Interaction includes communication between the researcher and the subject or the collection of private information/data from a third party including medical records or a family member.

Private information includes information about behavior where there is a reasonable expectation by the individual that no observation is taking place, or information (such as medical information from a patient chart) that individuals can reasonably expect will not be made public and which is individually identifiable.

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

[Portions taken from 45 CFR 46.102].

CHAPTER 4

Categories of Research Review

POLICY:

A. Exempt Research

Exempt Research refers to research meeting certain criteria [as outlined in 46 CFR 46.101(b)]. Research meeting this criteria is not subject to continuing review. The determination as to whether or not a project is exempt must be made by the staff of the IRB in conjunction with the IRB Chair or designee. The investigator does not have the authority to make this determination. The term exempt may be confusing because the project must in fact be submitted for review. Research being considered for exempt status are reviewed as they come in.

B. Expedited review

The expedited review procedure shall be used to review research activities that meet the criteria outlined in 45 CFR 46.110 and 21 CFR 56.110 . The expedited review procedure shall not be used to approve any research which includes genetic testing, or any Cooperative Group Protocol funded by the Federal Government and open to enrollment. Under the expedited review procedure, review shall be carried out by the IRB Chair or designee without a convened meeting of the full IRB committee. The IRB Chair or designee shall have the same authority as the IRB except they may not disapprove the research. A research activity may be disapproved only after full-board review.

The IRB will use the expedited review procedure to review research activities that:

- present no more than minimal risk to human subjects; and
- involve only procedures listed in one or more of the categories outlined below.

Minimal risk: the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. e.g., the risk of drawing blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examinations and does not exceed a certain amount.

The following categories of research have been provided by DHHS as areas of research which may qualify for expedited review. Although a specific research procedure may fall within these categories and be eligible for expedited review, the research might not be considered minimal risk after consideration by the expedited review procedure and may be referred to full IRB review.

Permissible Categories- which apply regardless of the age of subjects, except as noted:

- Clinical studies of drugs for which an investigational new drug application is not required.
- Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review. (e.g. the use of an approved

chemotherapy drug in cancer patients in combination with other approved drugs that may increase the risk to the patient when taken concurrently, or the use of an approved drug in a particularly vulnerable population).

- Clinical studies of medical devices for which:
    - an investigational device exemption application (21 CFR 812) is not required; or
    - the device is cleared/approved for marketing and is being used in accordance with its cleared/ approved labeling
- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from:

(**NOTE**: This does not include such specimens collected for genetic research.)

- healthy, non-pregnant adults who weigh at least 110 pounds (amounts drawn may not exceed 500 ml in an 8-week period, and no more than 5 such amounts per year; collection may not occur more than 2 times per week)
- healthy infants, children, and adolescents (amounts drawn may not exceed 7 ml per kg in an 8-week period, and no more than 5 such amounts per year)
- other adults and children, considering the age, weight and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected (amounts drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period; collection may not occur more frequently than 2 times per week).

NOTE: Protocols approved via the expedited review procedure in this category must not enroll patients who do not meet these criteria (e.g., a healthy, non-pregnant adult who is less than 110 pounds, etc.). Approval under this category automatically excludes subjects who do not meet the criteria as detailed above.

- Prospective collection of biological specimens by non-invasive means. Examples:

(**NOTE**: This does not include such specimens collected for genetic research.)

- hair and nail clippings in a non-disfiguring manner
- deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
- permanent teeth, if routine patient care indicates a need for extraction
- excreta and external secretions (including sweat)
- uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue
- placenta removed at delivery
- amniotic fluid obtained at the time of rupture of the membrane prior to or during labor
- supra- and sub-gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques
- mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings
- sputum collected after saline mist nebulization
- Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.

- Where medical devices are employed, they must be cleared/approved for marketing.
- Note: studies intended to evaluate the safety & effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared devices for new indications.
- Examples: physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; weighing or testing sensory acuity; magnetic resonance imaging; electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual

- Research involving materials (data, documents, records, specimens) that have been collected or will be collected solely for non-research purposes (e.g., medical treatment or diagnosis).

- Note: some research in this category may be exempt.

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

- Research on individual or group characteristics or behavior, including but not limited to:

- research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior; or
- research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: some research in this category may be exempt)

- Continuing Review of research previously approved by convened IRB:
    - where the research is permanently closed to enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or
    - where no subjects have been enrolled and no additional risks have been identified; or
    - where the remaining research activities are limited to data analysis.

- Continuing Review where categories above do not apply but IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

- Minor Changes in previously approved research during the period for which approval is authorized (e.g., changes where the risk to the subject is not increased; this may include such changes as change in sample size or in reimbursement for participation).

Note: The standard requirements for Informed Consent (or its waiver, alteration, or exception) apply regardless of the type of review utilized by the IRB.

For the review of new research protocols qualifying for expedited review, once the review has been completed, the Office of the IRB will send written correspondence with one of the following decisions, along with additional comments where appropriate:

- **Approval**: approved as submitted with no modifications required. The approval letter will include the date that the first progress report is due as determined by the IRB and any other conditions that apply.

- **Approval with revisions**: approved as revised by the IRB. The IRB has made revisions to the submission and approval is contingent upon the inclusion of these revisions. The approved version of the submission shall include any and all of the revisions made by the IRB, IRB Chair, or his designee.
- ***Minor modifications required**: protocol requires minor revisions that do not affect the safety of the research subject. The IRB chair/designee may approve the study upon receipt of the satisfactory revisions. If no revisions are received by the IRB within 120 days, the protocol is considered withdrawn.
- **Deferred**: either the protocol does not qualify for expedited review or substantive issues regarding the protocol and/or consent form must be addressed. Full IRB review of the protocol is required.

Similarly, a letter signed by the IRB Chair or designee outlining the decision shall be sent to the Principal Investigator when Progress Reports or other items pertaining to research are reviewed and approved through the expedited review procedure.

***NOTE: A protocol is not approved until <u>all</u> required modifications are received and approved by the IRB. There may be <u>no</u> activity on the project until these modifications have been approved by the IRB, and the approval letter has been received by the Principal Investigator indicating approval and permission to begin the project. The term of the approval will be indicated, as well as the date that the first progress report is due. Any special conditions that have been applied to the research will also be indicated in the approval letter. Each protocol will receive an IRB Number; this number must be included on all future correspondence.**

C. Full IRB Review

All new research protocols which are not exempt and which do not qualify for expedited review shall be reviewed <u>using the full IRB review procedure by a convened IRB</u>. All items related to ongoing research (amendments, revised consent forms, etc.) which do not qualify for expedited review will also be reviewed by the full IRB at a convened meeting.

D. Non Human Subjects Research Determination

Following receipt of submission materials, Asentral IRB will determine whether the proposed acticity meets the regulatory definition of human subjects research as defined by FDA 21 CFR 50.3(c0 and (g);21 CFR 56.102© and (e0; 21 CFR 312.3(b);21 CFr 812.3(h) and (p) and DHHS 45 CFR46.102(d) and (f). A study must involve both "human subjects and "research"according to the regulations to be considered human subjects research. If a study is subject to both FDA and DHHS regulations, and is considered human research under only one category, the study must still receive IRB review under the regulations that classify it as human subjects research.If the study is determined to be non human subjects research, the sponsor and/or investigator will be notified within 48 hours of this determination.

E. The Appeal Process

A Principal Investigator may appeal a decision made by the IRB within 120 days of the date of the decision letter from the IRB. The appeal must be made in writing and sent to the IRB Chair or Office of the IRB. The Chair and Office of the IRB will review the materials submitted and decide whether additional information is necessary to present at the IRB meeting. The appeal will be brought to the next convened meeting of the IRB. The Chair may invite the Principal Investigator to attend the meeting to give a presentation of the protocol and to address problematic issues. Written notification of the IRB's decision of the appeal will be sent to the Principal Investigator following the meeting.

A decision for disapproval after appeal is final. If significant modifications are made to a previously disapproved protocol, it may be submitted as a new protocol. The IRB Chair has the authority to determine whether a previously disapproved protocol has been amended sufficiently to warrant review as a new protocol.

CHAPTER 5

Continuing Review

A. Continuing Review of Ongoing IRB-approved Research

The IRB shall conduct continuing review of all research activity in compliance with 45 CFR Part 46 and 21 CFR Part 56. Continuing review is required for all research protocols approved by the IRB, (unless the protocol was determined to be exempt by the IRB at submission) for the duration of the research, at least as long as **individually identifiable** follow-up data are being collected or analyzed, and regardless of whether a protocol has been closed to patient enrollment or whether the treatment portion of the research is complete. Continuing review includes, but is not limited to, progress reports, annual renewals, five-year renewals, compliance audits, routine audits, amendments, safety reporting, and study closure, and any other activity which the IRB determines necessary for monitoring ongoing research.

B. Annual Reports

Federal regulation limits the period for which a research protocol can be approved to a maximum of 365 days.

In order to renew the approval period for a protocol, it is the responsibility of the principal investigator to submit a progress report and relevant documents as required by the IRB.

It is the PI's responsibilty to obtain continuing approval in a timely manner. Therefore, the site should maintain internal systems to track when continuing reviews must be submitted. Although there are IRB reminders to the sites, they should not be relied upon to avoid lapses in approval

The expiration date for an IRB protocol is the first date that the protocol is no longer approved If a PI has failed to provide continuing review information to the IRB or the IRB has not reviewed

and approved a research study by the expiration date specified by the IRB, such a research study has expired. . If the IRB has not approved the protocol on the expiration date cited on the most recent Notice of IRB Approval, the IRB approval expires automatically and all study activities must cease.

It is the responsibility of the Principal Investigator to submit progress reports in a timely fashion.

Annual reports are requested by the Office of the IRB approximately 1 month prior to a project's expiration date, with a second notice requested at 2 weeks prior to the expiration date if the report has not yet been received. If a progress report is not received by the due date or the IRB has not reviewed and approved a research study by the expiration date, such a research study has expired.

If the protocol approval lapses, the IRB may require either re-consent of affected subjects for continued study participation, or documentation of written permission from the affected subjects for use of any research data collected during the period of approval lapse, as solely determined by the IRB.

The IRB may also require that the PI submit a Protocol Deviation/Violation Report that will explain the circumstances of the approval lapse and the plan to prevent a future lapse.

This expiration of IRB approval is not reported to OHRP or FDA as a suspension or termination of IRB approval under DHHS or FDA regulation. If no written reply is received from the PI to the Notice of Expiration of the IRB Approval within 30 days post-expiration date, a Notification of Study Termination is issued. The study can only be re-opened by submitting a new application which requires convened IRB's approval.

*NOTE: For the safety of research subjects who are enrolled in research projects in which investigational therapy is being administered, Federal guidance indicates that short-term continuation of the therapy beyond the IRB approval date, if the investigator is actively pursuing renewal with the IRB, and the IRB believes that an over-riding safety concern or ethical issue is involved, may be permissible. There must be notification to the IRB Office of all such situations, including a justification for each subject whom the investigator wishes to continue on an investigational therapy while the study is in the process of being reinstated. It is critically important that the investigator reinstate the protocol rapidly (see Reinstatement of Terminated Protocol). When study approval is terminated by the IRB, in addition to stopping all research activities, any subjects currently participating should be notified that the study has been terminated. (FDA Information Sheets, 1998 Update, Continuing Review After Study Approval).

Should an annual report be received prior to the expiration date but is found to be deficient, the IRB shall contact the investigator with details regarding the deficiencies. If a complete and correct progress report is not received within the required time-frames, the project is considered expired and subject to the same procedures outlined above. The IRB is not authorized to extend the approval period for any research project.

C. Five-Year Renewals

A project may be renewed annually (or at more frequent intervals) for up to five years following initial approval, after which time, if the investigator elects to continue the research, submission of the protocol to the IRB will be required for review as a new protocol. The renewal application must include a report of the progress to date.

D. Reinstatement of Terminated Protocols

A protocol which was previously terminated may be reinstated only after review and approval of the protocol by the convened IRB. If a protocol which was previously approved by the IRB was closed due to administrative reasons (e.g. delinquent progress reports), the only mechanism which exists to issue approval for the protocol to continue is review by the convened IRB as if the protocol was a new submission. The IRB does not have the authority to extend the approval period for a study, or to reinstate a protocol without review by the convened IRB.

In order to reinstate a previously terminated protocol, the Principal Investigator must submit a complete IRB application packet in accordance with the requirements for new protocols (see Protocol Submission).

For studies which were terminated for administrative reasons (i.e. delinquent progress reports, etc.) in addition to the protocol application the Principal Investigator must submit a memorandum to the IRB detailing the circumstances that led to the protocol closure, along with the corrective action which has been taken in order to avoid such closures in the future.

E. Compliance Audits

The IRB shall request additional information if necessary, outside of the normal request for progress reports, in order to ensure that the rights and welfare of research subjects are protected. The IRB or IRB Chair/designee shall have the authority to initiate the process for evaluating a protocol in order to immediately address a potential deficiency or situation which may pose a risk to participants. Additionally, the IRB or Chair/designee shall have the authority to suspend a protocol if deficiencies are noted that would pose a risk to potential or participating subjects.

If there is no response to an IRB decision for Modifications Required or Deferred within 120 days, the protocol is considered withdrawn

CHAPTER 6

Principal Investigator Responsibilities

Before a research project involving human subjects is initiated, it must first be reviewed and approved by one of the Asentral, Inc. IRBs, and then conducted according to the procedures and guidelines set forth in the Standard Operating Policies and Procedures of Asentral, Inc. IRB, which are consistent with Federal and State regulations governing research. IRB approval is required regardless of whether the study in question is to be supported by funds from outside granting agencies or private sources, or by Institutional funds, or considered to be minimal risk; approval is likewise required when no specific funding is involved.

The Principal Investigator of a clinical research study must accept the following responsibilities:

1. The researcher must be familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information , and in other information sources provided by the sponsor.
2. Ensuring that individuals involved in the conduct of the study are qualified by education, training, and experience to perform his/her respective task.
3. Protecting the rights and welfare of human research subjects. The health and well-being of the individual patient/subject must be the first priority.
4. Complying with all Federal, State and Institutional regulations as set forth in the Institutional Policies and Procedures, the Multiple Project Assurance, all other pertinent regulatory documents and their amendments.
5. Submitting each research activity to the Office of the IRB for determination as to whether it qualifies as exempt or needs expedited or full IRB review.
6. Ensuring proper execution of the informed consent process (see Informed Consent), including efforts to ascertain that the subject has comprehended the information in the consent form, as well as retaining all original, signed consent forms. The original consent forms should be retained in a secure file separate from the subject's study records. The most recently approved version of the consent form must be used when consenting a subject.
7. Ensuring that any proposed changes in previously approved research activities are submitted to the IRB and that no changes are initiated prior to IRB review and approval, except where necessary to eliminate immediate hazards to the subjects.
8. Submitting progress reports, as requested, in a timely fashion (see Progress Reports).

9. If the researcher terminates or suspends a clinical trial without prior agreement of the sponsor, the researcher informs the organization , sponsor, and the IRB.
10. Upon completion of a clinical trial, the researcher informs the organization; the IRB with a summary of the trial's outcome; and the regulatory authority with any reports required.
11. Complying with all decisions and requirements of the IRB.
12. Promptly reporting any serious, unanticipated problems involving risks to subjects or others to the IRB (see Safety Reporting).
13. Providing the IRB with accurate and up-to-date information regarding the research.
14. Ensuring that additional personnel are added to protocol when necessary in order to include the appropriate expertise for carrying out the protocol.
15. Attending or completing education and training sessions.
16. Ensuring that all appropriate key personnel involved in the design, implementation or analysis of the protocol are listed as co-investigators and have been adequately trained in good clinical practice and the protection of human subjects in research (and the responsible conduct of research). Investigators will be asked to declare their training on the Asentral, Inc IRB Study Application Form.
17. Key personnel are defined as, and should be limited to, individuals who contribute in a substantive way to the scientific development or execution of the project. This includes all investigators who meet this definition, including research coordinators and nurses. Consultants should be listed only when their level of involvement meets the definition of key personnel. Individuals providing technical services and who have no access to patient identifying information are not considered key personnel.

For clinical investigations sponsored by industry, in addition to all of the requirements set forth above the investigator must complying with all requirements set forth in the clinical protocol and contract. This includes the performance of all protocol-required testing, maintenance of complete and accurate records as per the sponsor's requirements, and complete and timely communication with the sponsor and IRB.

CHAPTER 7

Submitting to the IRB

The IRB shall review and shall have the authority to approve, require modification, or disapprove all research activities, including proposed changes in previously approved human subjects research. The IRB will comply with the Federal guidelines at 45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA), individual state regulations pertaining to research being conducted in that particular jurisdiction, and these IRB policies in order to determine whether protections for human research subjects are adequate. All new research protocols involving human subjects which do not qualify as exempt, as determined by the IRB Chair or a designee, will be reviewed using either expedited or full IRB review procedure. All other research activities (including continuing review, protocol and consent form modifications, adverse event reports, etc.) will also

be reviewed by either expedited or full IRB review procedure using criteria at 45 CFR 46.110 and 21 CFR 56.110.

In order for a protocol to be placed on the meeting agenda, it shall be submitted on or before the deadline date and conform to all of the following requirements. If the protocol is incomplete (does not conform to all requirements, including signatures, etc.), the IRB Office shall notify the Principal Investigator of the deficiencies.

Research protocols submitted for IRB review must have one principal investigator (PI) listed as well as all co-investigators who will be involved in the research; only those individuals so listed may recruit subjects and participate in the study.

A. New Protocol Submission

Below is a list of information and forms to be included in the IRB submission packet from the Principal Investigator and Sponsor/CRO. A review cannot be performed until all appropriate information has been received.

- Study Application Form
- Investigational Drug Brochure or Package Insert
- Study Protocol
- Informed Consent (*hard copy and diskette-Microsoft Word compatible*)
- Proposed Subject Information (*if any*)
- Copy of the signed Form FDA 1572
- Satellite Site Application(s) for each site listed in section #3 of the Form FDA1572 (if applicable)
- Shipping & Invoicing Information Form
- Proposed Advertising/Recruitment material (*if any*)
- Curriculum vitae (CV) of the Principal Investigator and all Sub-Investigators
- (CVs must be current within 1 year, include any medical license informationand be signed and dated) (**Massachusetts** sites please include the Massachusetts Research Registration Number from the Department of Public Health for the PI)
- Financial Disclosure form of Principal Investigator and all Sub-Investigators listed on the Asentral, Inc. IRB Application Form.

B. Amendments

No deviations from, or changes to, a protocol shall be initiated without prior IRB approval of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involve(s) only logistical or administrative aspects of the trial [e.g., change of monitor(s), telephone number(s)]. When changes are implemented to eliminate an immediate hazard, or to change logistical administrative aspects of the trial, the IRB must be notified of the change promptly.

Minor changes are defined as: (1) changes that do not alter the overall risk-benefit profile of the study; (2) changes that would not potentially affect the willingness of enrolled subjects to remain in the study, or the willingness of potential subjects to enroll in the study; and (3) changes that do not alter the scientific validity of the study design

The investigator must **promptly** (within 3-5 business days) report (1) any deviations from, or changes to, the protocol for the purpose of eliminating immediate hazards to the trial subjects, (2) changes which alter the risk/benefit ratio for study subject(s) and/or which significantly affect the conduct of the trial, and (3) new information that may affect the safety of the subjects or the conduct of the trial.

In addition, the IRB requires that the investigator submit, in a timely manner, all other protocol amendments, revised consent forms, adverse events, changes in investigators, changes to FDA Form 1572 (for clinical trials), and any other information which may affect the conduct of the research study.

Minor changes in the protocol and/or consent form may be reviewed through the expedited review procedure (see Expedited Review). However, when a proposed change is not minor it will be reviewed by the IRB at a convened meeting.

The original approval date for the protocol remains as the reference point for continuing review requirements (i.e. the amendment does not change the expiration date of the project.)

All such study modifications must be reported to the IRB. This submission should include an explanation of the modification and its impact on the risk/benefit assessment written by the Principal Investigator.

C. Reporting Protocol Violations

Protocol Deviations are defined as any departure or change from the protocol that is unanticipated and happens without any prior agreement.

Asentral, Inc. IRB requires that all major protocol deviations be reported. Major Protocol Deviations are considered to be protocol deviations that:

- Adversely affect the safety, rights or welfare of subjects or others
- Adversely affect the integrity of the study data

Deviations that have occurred repetitively or might occur again may also qualify as significant deviations and should be reported to Asentral, Inc. IRB (if it is anticipated that this violation will occur again, an amendment to the protocol should be considered).

Significant protocol deviations need to be reported to Asentral, Inc. IRB promptly, but no later than ten (10) business days from the date the site became aware of the event.

Investigators are responsible for conducting human-subjects research in accordance with all applicable federal and state regulations and the Asentral, Inc. Institutional Review Board (IRB) policies and procedures. During the conduct of the study, changes to the protocol may be proposed or unintentional changes may be discovered. Changes to the IRB-approved protocol, planned or otherwise, are governed by federal regulations and Asentral, Inc. IRB policies and procedures.

The federal regulations specifically require the IRB to review proposed changes in an approved research project, and assure that these changes are not initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [45CFR46.103(b)(4)(iii) and 21CFR56.108(a)(4)]. Research activity includes all aspects of the conduct of the research study, e.g., recruitment methods, consent process,

procedures used to protect privacy and confidentiality, etc. – all of the information outlined in the protocol submission and reviewed and approved by the IRB. Non-compliance with these regulations or Asentral, Inc. IRB policies, procedures, or requirements during the conduct of a research study results in a protocol violation, and as such must be reported to the IRB.

In general, a protocol violation is a deviation from the research plan of activity that may impact subject safety, affect the integrity of the study data, and/or affect the willingness of the subject to participate in the study. Essentially, any deviation from the protocol is, in effect, a protocol violation that must be reported to the IRB. The Asentral, Inc. **IRB Unanticipated Problem/Event Report Form** is to be used to report protocol violations: deviations from the IRB-approved protocol that are not approved by the IRB prior to initiation or implementation. [For planned changes to the IRB protocol, please submit a formal protocol amendment or modification to Asentral, Inc. IRB. Such planned changes must be approved prior to initiation or implementation of the change.]

REPORTING REQUIREMENTS
Protocol violations must be reported to Asentral, Inc. IRB within 10 working days of discovery using this form with the exception of the following conditions which require the Investigator to report promptly (within 3-5 business days):

- Any deviations from, or changes to, the protocol for the purpose of eliminating immediate hazards to the trial subjects
- Changes which alter the risk/benefit ratio for study subject(s) and/or which significantly affect the conduct of the trial, and
- New information that may affect the safety of the subjects or the conduct of the trial.

Reports of protocol violations should be submitted to the sponsor as outlined in the sponsor's protocol.

Planned Protocol Deviations

In general, all planned protocol deviations must be submitted to the IRB for review and approval prior to implementation; except where necessary to eliminate apparent immediate hazards to the human subjects.

However, if the research is a clinical investigation of a device, and the research is not federally funded, and the research is not conducted under an FWA, then only planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to the IRB for review and approval prior to implementation; except where necessary to eliminate apparent immediate hazards to the human subjects.

Subsequent Actions by the IRB Chair/Designee to determine if the problem or event meets the definition of an UPIRTSO

Any such incident, experience or outcome generally will warrant consideration of a quality improvement (corrective) action, such as a change in the research protocol and/or consent document, in order to protect the safety, rights and welfare of research subjects.

1. If the IRB Chair/Designee determines that the problem is not a UPIRTSO:

No further action is taken under this policy and procedure.

2. If the IRB Chair/Designee determines that the problem is an unanticipated problem involving minimal risk to subjects or others:

The Chair/Designee can require minor modifications to the research (as defined under 2.1 Expedited Review: PROCEDURE) or follow the procedure for unanticipated problems involving more than minimal risk to subjects or others.

3. If the IRB Chair/Designee determines that the problem is an unanticipated problem involving more than minimal risk to subjects or others:

(a) The IRB administrator places the matter on the agenda at the next available IRB meeting.

(b) The IRB administrator provides all members with a copy of the report, the IRB application, the currently approved IRB protocol summary, and the currently approved consent documents. All IRB members are expected to review these materials. The primary reviewer is additionally provided a copy of the investigator brochure and any previous reports of unanticipated problems involving risks to subjects or others related to the protocol.

(c) The convened IRB considers the following actions:

- Suspension of the study
- Termination of the study
- Modification of the protocol
- Coordination of care planning with clinical staff
- Revised plan for research staff competencies, roles and/or responsibilities
- Referral to institutional safety officer for root cause analysis and quality improvement plan
- Other appropriate quality improvement action plan
- Modification of the information disclosed during the consent process
- Providing additional information for current or past subjects
- Re-consent of current subjects taking part in the study.

4. The IRB has to report the following events to FDA and OHRP:

- Unanticipated problems involving risks to participants or others
- Serious and continuing non-compliance
- Suspensions and terminations

D. Safety Reporting

DEFINITIONS

Adverse event (AE)

An **adverse event** is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with enrollment in a research study, whether or not considered related to the product, device, or treatment being tested.

Unexpected Adverse Experience

Unexpected adverse experience: any adverse experience that is not identified in nature, severity or frequency in the current investigator brochure; or, if an investigator brochure is not required, that it is not identified in nature, severity or frequency in the risk information described in the general Investigational Plan or elsewhere in the current research application.

In accordance with Federal regulations, the IRB requires that any serious, unexpected problems involving risks to subjects or others be promptly reported to the IRB, , and the sponsor. This reporting is in addition to, and does not supplant, periodic progress reports (see Annual Reports).

The IRB or IRB Chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB Chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the Principal Investigator. The IRB or IRB Chair/designee shall promptly report it's findings to the investigator, Institutional officials, the sponsor, Office of Human Research Protection (OHRP), and the FDA if an investigational drug or device is involved.

Asentral, Inc. IRB requires that **Serious Adverse Events (SAE's)** be reported to the IRB by the sites when they meet the following criteria:

- The event is serious. An event is considered serious if it results in any of the following outcomes:
  - death
  - a life threatening situation
  - requires hospitalization
  - a significant incapacity or substantial disruption of the ability to conduct normal life functions
  - a congenital anomaly or birth defect
  - it presents, in the judgment of the investigator, as a situation that requires medical or surgical intervention to prevent one of the outcomes listed above
- The event, in the judgment of the Investigator, is related to the study drug, device or study procedures.

If the adverse event meets both of these requirements, it is reportable to the IRB as an SAE. Investigators are required to report SAE's to Asentral, Inc. IRB within ten (10) business days of becoming aware of them. An adverse event that does not meet both criteria as stated above does not need to be reported to the IRB.

Additionally, FDA requires that sponsors notify all participating investigators of any adverse event associated with the use of a test article that is both serious and unexpected that occurs at one of the participating sites. These reports must be reported to the IRB by the investigator as they are received. Additionally, if reports are received by an investigator in the form of a periodic Data Safety Monitoring Board Report (often a compilation of adverse events), the investigator shall provide a written summary to the IRB along with the DSMB report.

Some industry-sponsored protocols have more stringent definitions and/or reporting requirements. In this case, the requirements set forth in the protocol must be followed.

NOTE: It is generally recommended that the term "side effect" not be used synonymously with "adverse event".

PROCEDURE:

Adverse events and/or laboratory abnormalities identified during the protocol as critical to safety evaluations should be reported to the sponsor and the IRB according to the reporting requirements and within the time periods specified by the sponsor in the protocol (if specified). If no time period is specified by the sponsor for a particular protocol, the general interval reporting periods set forth above are appropriate.

For reported deaths, the investigator must supply the sponsor and the IRB with any additional requested information (e.g. autopsy reports and terminal medical reports).

F. Unanticipated Problems

DEFINITIONS

Adverse event (AE)

An **adverse event** is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with enrollment in a research study, whether or not considered related to the product, device, or treatment being tested.

Unexpected Adverse Experience

Unexpected adverse experience: any adverse experience that is not identified in nature, severity or frequency in the current investigator brochure; or, if an investigator brochure is not required, that it is not identified in nature, severity or frequency in the risk information described in the general Investigational Plan or elsewhere in the current research application.

In accordance with Federal regulations, the IRB requires that any serious, unexpected problems involving risks to subjects or others be promptly reported to the IRB, institutional official, and the sponsor. This reporting is in addition to, and does not supplant, periodic progress reports (see Progress Reports).

The IRB or IRB Chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB Chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the Principal Investigator. The IRB or IRB Chair/designee shall promptly report its findings to the investigator, Institutional officials, the sponsor, Office of Human Research Protection (OHRP), and the FDA if an investigational drug or device is involved.

All serious and unexpected adverse events which occur during a study at sites reviewed by this IRB, or in a post-study period of reasonable duration, should be reported to the IRB and the study sponsor, as appropriate, within 2 business days of occurrence or knowledge of event by the investigator.

Additionally, FDA requires that sponsors notify all participating investigators of any adverse event associated with the use of a test article that is both serious and unexpected that occurs at one of the participating sites. These reports must be reported to the IRB by the investigator as they are received. Additionally, if reports are received by an investigator in the form of a periodic Data Safety Monitoring Board Report (often a compilation of adverse events), the investigator shall provide a written summary to the IRB along with the DSMB report. Change this to match approval letter language

Some industry-sponsored protocols have more stringent definitions and/or reporting requirements. In this case, the requirements set forth in the protocol must be followed.

NOTE: It is generally recommended that the term "side effect" not be used synonymously with "adverse event".

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) that Require Prompt Reporting to IRB

This applies to non-exempt human subjects study and provides guidance on the protection of human research subjects at 45 CFR part 46 related to the review and reporting of unanticipated problems involving risks to subjects or others. In particular, this policy clarifies that only a small subset of adverse events occurring in human subjects participating in research are unanticipated problems that must be reported under 45 CFR part 46. The policy is intended to ensure that the review and reporting of unanticipated problems occur in a timely and meaningful way so that human subjects can be better protected from avoidable harms.

Federal regulations require prompt reporting to the Institutional Review Board (IRB), sponsor, and the appropriate regulatory agencies of unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study. (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)).

Definitions

1. Unanticipated Problems:

- In general, Unanticipated Problems include any incident, experience, or outcome that meets all of the following criteria:
- Unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the subject population being studied;
- (Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research). Asentral IRB interprets "reasonable possibility" to mean "more likely than not". Therefore "possibly related" means "more likely related than unrelated"; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

2. Adverse Events:

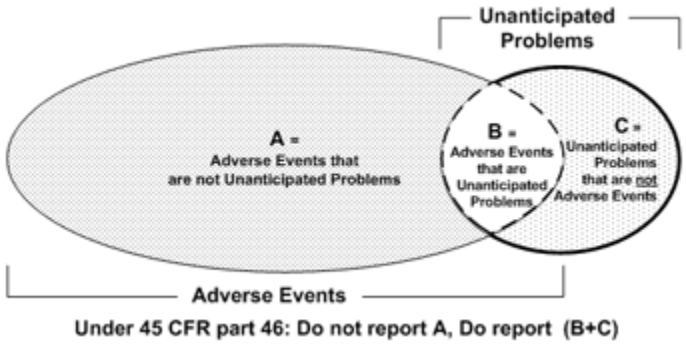
The term adverse event in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

3. Relationship between Unanticipated Problems and Adverse Events

The relationship between unanticipated problems and adverse events is illustrated in the diagram below:



Under 45 CFR part 46: Do not report A, Do report (B+C)

4. External event

From the perspective of one particular institution engaged in a multicenter clinical trial, external events are those events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

5. Internal event

From the perspective of one particular institution engaged in a multicenter clinical trial, internal events are those events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all events would be considered internal events.

6. Serious Adverse Experiences or Events that Require Prompt Reporting

A serious adverse experience or event requires prompt reporting when it meets all of the 3 following criteria:

(a). Unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the subject population being studied;

(b). Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(c). Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7. Non-serious Adverse Experiences or Events that Require Prompt Reporting

A non-serious adverse experience or event requires prompt reporting when it meets all of the 3 following criteria:

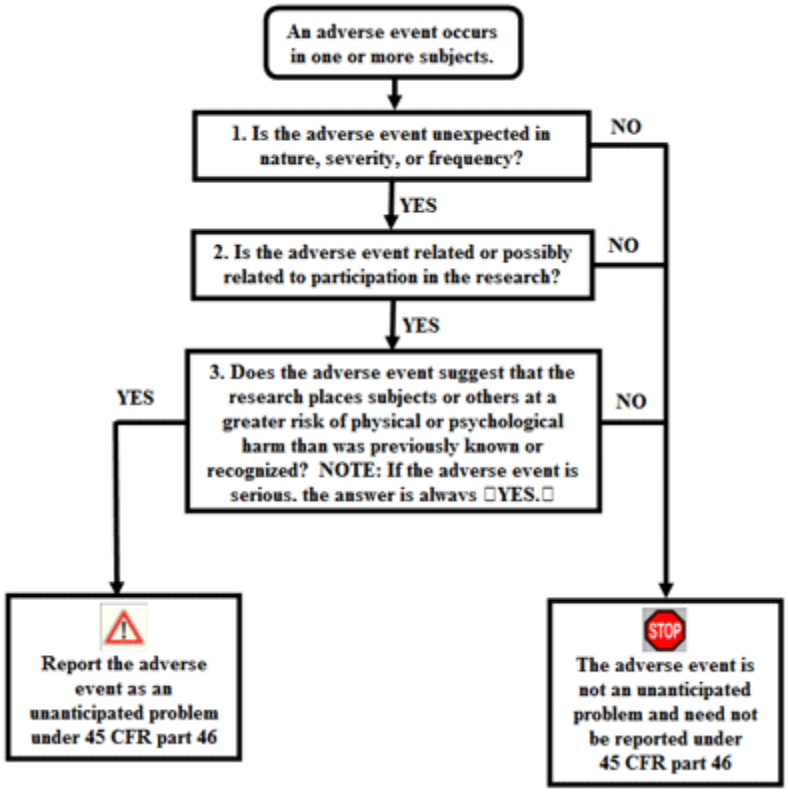
(a). Unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the subject population being studied;

(b). Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(c). Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Determining if an Adverse Event is an Unanticipated Problem

In order to determine if an adverse event represents an unanticipated problem that needs to be reported under HHS regulations 45 CFR part 46, follow the algorithm in the following flow chart:



Problems/Events that Require Prompt Reporting to the IRB

- The PI is required to promptly notify the IRB of any of the following problems:
- Any adverse event that as described above requires prompt reporting to the IRB.
- Information that indicates an adverse change to the risks or potential benefits of the research.
- For example:
- An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.
- A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
- Allegation of non-compliance with protocol requirements (including protocol deviations or violations) or IRB policies.
- Breach of privacy or confidentiality.
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Incarceration of a subject in a protocol not approved to enroll prisoners.
- Sponsor imposed suspension for risk.

- Complaint of a subject when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Any departure from the protocol (deviation or violation) that harmed subjects or others; that indicates subjects or others might be at increased risk of harm; or that compromises the integrity of the research data.
- Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or frequency in the investigational plan or application [including a supplementary plan or application], or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)
- An event that, as dictated by the protocol, requires urgent reporting to the sponsor
- Any change made to the research without prior IRB approval in order to eliminate apparent immediate harm
- Any safety reporting requirements specified by the IRB as a condition of approval.
- Any other problem that the investigator considers to be unanticipated and indicates that subjects or others are at increased risk of harm.

2. The reporting may occur at one of three different times:

(a) Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via e-mail or fax by providing a brief summary of the event. Then, within 1 week (five business days), study personnel will send to the IRB a Safety Event submission.

(b) For a reportable serious adverse event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission.

(c) For any other problem or event requiring prompt reporting to the IRB, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission.

(F). Subsequent Actions by the IRB Chair/Designee to determine

if the problem or event meets the definition of an UPIRTSO

Any such incident, experience or outcome generally will warrant consideration of a quality improvement (corrective) action, such as a change in the research protocol and/or consent document, in order to protect the safety, rights and welfare of research subjects.

1. If the IRB Chair/Designee determines that the problem is not a UPIRTSO:

No further action is taken under this policy and procedure.

2. If the IRB Chair/Designee determines that the problem is an unanticipated problem involving minimal risk to subjects or others:

The Chair/Designee can require minor modifications to the research (as defined under 2.1 Expedited Review: PROCEDURE) or follow the procedure for unanticipated problems involving more than minimal risk to subjects or others.

3. If the IRB Chair/Designee determines that the problem is an unanticipated problem involving more than minimal risk to subjects or others:

(a) The IRB administrator places the matter on the agenda at the next available IRB meeting.

(b) The IRB administrator provides all members with a copy of the report, the IRB application, the currently approved IRB protocol summary, and the currently approved consent documents. All IRB members are expected to review these materials. The primary reviewer is additionally provided a copy of the investigator brochure and any previous reports of unanticipated problems involving risks to subjects or others related to the protocol.

(c) The convened IRB considers the following actions:

- Suspension of the study
- Termination of the study
- Modification of the protocol
- Coordination of care planning with clinical staff
- Revised plan for research staff competencies, roles and/or responsibilities
- Referral to institutional safety officer for root cause analysis and quality improvement plan
- Other appropriate quality improvement action plan
- Modification of the information disclosed during the consent process
- Providing additional information for current or past subjects
- Re-consent of current subjects taking part in the study.

(d) The Institutional Official is notified.

F. Closure of A Protocol

The principal investigator must notify the IRB of the termination/suspension of a protocol.

The IRB Chair/designee shall notify the PI of any protocol which is terminated/suspended by the IRB or IRB Chair due to delinquent progress reports, concern for safety of human subjects, non-compliance, etc.

The following are two different mechanisms by which a protocol may be closed:

1. Voluntary closure by the investigator or sponsor (study ends, investigator leaves the institution, etc.)
2. IRB closes the study due to safety concerns or delinquent progress reports (failure to renew a protocol prior to expiration of IRB approval).

The Principal Investigator may submit a memo to the IRB providing a summary report and detailing the reason for study closure. If the study closure occurs at the same time that a progress report is due, the investigator may close the protocol via the progress report form, as long as all of the questions on the form are completed.

The IRB will formally acknowledge the closure of a study by the Principal Investigator or sponsor in writing.

The IRB will notify the Principal Investigator in writing of any decision to terminate a protocol outside of a request by the Principal Investigator or sponsor to do so.

G. Withdrawal of a Protocol

If a Principal Investigator changes his intent to conduct the study it may be voluntarily withdrawn.

CHAPTER 8

Informed Consent

A. Overview

No investigator shall involve a human being as a subject in research unless the investigator has obtained the approval of the IRB. The legally effective informed consent of the subject or the subject's legally authorized representative* shall be required, except when a waiver is granted under FDA and OHRP guidelines (as described below). All consent forms shall conform with 45 CFR 46.116, 21 CFR 50.20, and Institutional requirements.

The ethical principle of respect for persons is maintained by the process of informed consent from human subjects involved in research, and is a necessary process to help ensure that research is conducted in an ethical manner.

- Obtaining and maintaining Informed Consent is an ongoing process.
- An investigator shall seek such consent using the most recently approved version of the consent form under circumstances which provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate. **Coercion or undue influence** must be avoided.
- The information that is given to the subject or representative shall be in language understandable to the subject or representative. This means that the consent form must be translated into a language that they can understand, and the accuracy of that translation should be verified. (See Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English)
- 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.
- Each subject must be given a copy of the consent form to keep.

***Legally Authorized Representative**: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the research study. Authorized individuals include the parents or guardians of a minor, or a health care agent or guardian appointed pursuant to state law. Next of kin does not automatically qualify as a legally authorized representative (See Research Involving Incapacitated or Decisionally Impaired Subjects).

The following describe the required elements of informed consent as per federal regulation, as well as situations where the requirement of obtaining or documenting informed consent may be waived.

- Informed consent is a process that is documented by a consent form. The process should include an interaction between the investigator and the subject in order to ensure, to the best of the investigator's ability, the subject's comprehension of the protocol and, where possible, the investigator should document the process in the subject's medical record and/or research record.
- Informed consent is not valid unless the subject or the subject's legally authorized representative is fully informed about all the information in the consent document; the investigator should take notes where possible to indicate their general impression of the subject's understanding, including any questions that have been raised during the consent process.
- Signatures on consent forms do not absolve the investigator of their responsibility to make sure that the subject or the subject's legally authorized representative is fully informed about the research. Signatures on the consent form should be the culmination of the initial consent process.
- Except where a waiver is granted, obtaining initial informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. All potential research participants should be provided with the information in the IRB approved consent form both verbally and in a copy of the document itself. They must be

given ample time to think about whether or not they wish to participate, and must have the opportunity to ask questions. Ideally, the potential subject should be given the form to take home, and should be advised to think about their participation and discuss it with family and friends.

- If consent is obtained on the same day that research procedures are initiated, the investigator should document in the research record the date and time that consent was obtained and that it occurred prior to the initiation of the research procedures.
- Once a subject agrees to participate, the subject or the subject's legally authorized representative signs and dates the consent form in the appropriate place. The person obtaining consent (see Persons Authorized to Obtain Informed Consent from Research Participants) also signs the form and, in so doing, affirms that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives their consent to participate in the study. Consent for research procedures involving a medical or psychiatric intervention must be obtained by a physician member of the medical staff. The signature of a witness who observed the subject signing the consent form is necessary on all consent forms. The IRB may determine for a particular protocol that there must also be a witness to the entire consent process, which would be indicated as a condition of approval in the IRB's decision letter.
- One copy of the consent form must be given to the person signing the form (subject or representative) and a second copy should be placed in the subject's medical chart (if appropriate). The original, signed consent form must be retained in the P.I.'s research records. Consent forms must be retained for all subjects enrolled in the study, regardless of whether they withdraw or are withdrawn. A subject is considered enrolled at the moment they sign the consent form, whether or not they actually participate in the research or any of the procedures involved.

Federally Mandated Elements of Informed Consent

The following are the OHRP guidelines regarding informed consent which all researchers are required to follow. Institutional requirements and additional guidance for writing a consent form are outlined in a document entitled Guidelines for Preparing Research Consent Forms: Required and Suggested Language. This document provides guidance in preparing a consent document which will comply with the Federal requirements as set forth below, as well as the IRB requirements

B. **Basic Elements of Informed Consent**
(45 CFR 46.116)

In seeking informed consent the following information shall be provided to each subject:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- A statement describing the Institution's policy on liability for research related injury
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to the subject and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

C. **Additional Elements of Informed Consent**

When appropriate, one or more of the following elements of information shall also be provided to each subject:

- 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 or father a child) which are currently unforeseeable.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new finding developed during the course of the research which may relate to the subject's willingness to continue to participate will be provided to the subject.
- The approximate number of subjects involved in the study.
- If there is a potential for marketed products resulting from the research, a statement should be included which explains that the subject will not share in any profits or losses.

- If a study sponsor agrees to reimburse for research-related injury, such a statement should be added following the Hospital's standard policy for such.

- Such other information which the IRB recommends as meaningfully adding to the rights and protection of subjects.

D. Waiver of Informed Consent Requirements

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent in instances where the IRB finds and documents that certain criteria (as listed below) are met. Any waiver that is requested will be considered by the IRB on a case-by-case basis within the framework of the following criteria. The IRB may decide not to grant a waiver, and to require all of the elements of consent, for protocols which appear to meet this criteria if it determines that doing so is in the best interest of the subjects.

A complete waiver of informed consent can only be granted if:

- the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in methods or levels of payment for benefits or services under those programs; and

- the research could not practicably be carried out without the waiver or alteration.

or

- **the research involves no more than minimal risk to the subjects; and,**

- **the waiver or alteration will not adversely affect the rights and welfare of the subjects; and,**

- **the research could not practicably be carried out without the waiver or alteration; and,**

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

- **the research could not practicably be conducted without access to and use of the protected health information; and,**

- **The privacy risks to individuals whose protected health information is to be used or disclosed are reasonable in relation to the anticipated benefits, if any, to the individuals, and the importance of the knowledge that may reasonably be expected to result from the research; and,**

- **There is an adequate plan to protect the identifiers from improper use and disclosure; and,**

- **There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law; and**

- **There are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA regulations.**

NOTE: The informed consent requirements in this policy are not intended to preempt any applicable Federal, State or local laws which require additional information to be disclosed in order for informed consent to be legally effective. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent that the physician is permitted to do so under applicable Federal, State or local law.

The IRB will use the criteria above in determining whether or not the consent requirement can be waived. The Principal Investigator must include a request for such a waiver in the IRB application and must provide justification for the request.

E. Waiver of Documentation of Informed Consent

The IRB shall use the criteria in 45 CFR 46.117(c) when considering a request for waiver of documentation of informed consen

Consistent with 45 CFR 46.117(c), the IRB may **waive the requirement for the investigator to obtain a signed consent form** from some or all subjects if it finds either:

- 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; or

- 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 where the documentation requirement is waived, the IRB may require that a written statement summarizing certain elements be provided to the subject. A waiver of signed consent does not exempt an investigator from obtaining informed consent.

Example: A research project is being conducted in IV drug abusers who are infected with HIV. The study involves a survey which asks questions related to previous drug use, HIV status, and other potentially sensitive questions. The investigators do not need to know the names of the subjects, and the surveys can be completed anonymously. The only record linking an individual to the study would be the consent document itself. In this situation, the requirement for written consent may be waived in order to avoid the confidentiality risk.

[See Emergency Use Exemption from Prospective IRB Approval for additional exceptions to informed consent requirements in an emergency setting.]

The IRB will use the criteria above in determining whether or not the documentation of the consent requirement can be waived. The Principal Investigator must include a request for such a waiver in the IRB application.

E. Persons authorized to obtain informed consent from research participants

Informed consent for research involving medical/psychiatric intervention shall be obtained by a physician member of the medical staff who is familiar with all aspects of the research protocol, unless an exception is made by the IRB which allows for consent to be obtained by another investigator who is licensed to perform the intervention (e.g., RN, PA, etc.). Consent for research that does not involve medical/psychiatric intervention may be obtained by any investigator, including an investigator who is not a physician, if that individual is familiar with all aspects of the research protocol and is listed on the protocol as a research investigator.

[Intervention includes physical procedures and manipulations of the subject or the subject's environment for research purposes.]

In either case, the individual obtaining consent shall be listed on the protocol as either principal investigator or co-investigator.

The person obtaining consent signs the form, and in so doing attests that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives their consent to participate in the study.

F. Persons authorized to give permission for a subject (other than themselves) to participate in research

Consent, or agreement to participate in a research study, shall be given by the individual who will be the research subject or a person who is permitted to act on behalf of that individual (a legally authorized representative). Persons consenting on their own behalf must be an adult over the age of 18 years whose clinical condition does not preclude them from making a sound judgment regarding the risks/benefits of participation. For adult subjects incapable of consenting to participation due to their clinical or mental condition, permission may be obtained by the subject's legally authorized representative or, **in limited cases**, next of kin (See Research Involving Incapacitated or Decisionally Impaired Subjects.

For children, the parent or legal guardian shall be permitted to act on behalf of the child and give permission for their participation. However, the assent of the child shall be obtained from any child considered mature enough to understand (usually in the range of 7-9 years of age), unless

the IRB determines that the assent requirement can be waived (see Waiver of the Assent Requirement).

All research involving children as subjects shall be placed into one of the four categories of risk as outlined at 45 CFR 46.404-407. The categories are as follows:

1. 46.404 Research not involving more than minimal risk.
2. 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
3. 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield general knowledge about the subject's disorder or condition.
4. 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (Approval of research included under this category is very rare). **NOTE: Research in this category needs approval of the Secretary – DHHS in addition to IRB approval**.

Where research is covered under Category 3 or 4 (45 CFR 46.406 or 45 CFR 46.407), and when permission is to be obtained from parents, **both** parents shall 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. In this case, when only one parent is giving permission, the justification for not requiring the other parent's signature shall be documented in the research record and on the consent form. When research is covered under Category 1 or 2 (45 CFR 46.404 or 45 CFR 46.405), the permission of one parent shall be considered adequate unless the IRB indicates otherwise in its approval letter.

G. Waiver of the Assent Requirement

The IRB may grant a waiver for the assent requirement when it is determined that there is a prospect of direct benefit, no standard approved therapy exists which is equally effective, and the child may not have the ability to understand the ramifications of not participating. (See Research Involving Children).

H. Reconsenting Subjects

The need to re-consent patients when changes are made to a consent form for an ongoing study shall be determined by the IRB on a case-by-base basis, depending on the nature of the protocol and the changes that have been made. In some cases it may be appropriate to provide the subject with an addendum to the original consent form which provides the new information, or to verbally inform subjects of an administrative or other minor change with documentation in the medical record that such notification took place. If an addendum is used, it must clearly state that the information in the original consent form is still current and valid, and that the information is the addendum is supplementary.

Subjects shall be re-consented if:

- The consent form has been altered or amended since the subject signed the document and the changes are more than administrative (i.e. the information which has been added/deleted may have an impact on that subjects willingness to participate)

- The subject was a minor at the time of entry into a study and has since reached the age of 18.

- The subject was incapacitated at the time of enrollment and has now regained capacity (See Research Involving Incapacitated or Decisionally Impaired Subjects).

I. Expiration of Consent

The process of informed consent shall take place no more than 30 days prior to the initiation of the research. If more than 30 days has elapsed since the subject provided consent, the process shall be repeated. The same requirements for signatures and obtaining consent apply when re-consenting or presenting an addendum to a study subject.

J. Obtaining a Witness Signature

The IRB may require that the signature of a witness be obtained on research consent forms. In signing the consent form, the witness attests to the fact that they were present when the subject signed the consent form, not necessarily that they witnessed the entire consent process.

A witness may be anyone over the age of 18, and may be an employee of the hospital or a family member/friend. The use of patient's relatives/friends as witnesses is encouraged.

The IRB may also determine for a particular protocol that there must also be a witness to the entire consent process (as is the case for illiterate or particularly vulnerable subjects). Such a requirement would be indicated in the protocol approval letter.

K. Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English

The consent form shall be in a language understandable to the subject (or legally authorized representative). When non-English speaking subjects are to be enrolled into a study, a translation of the consent form should be available in their primary language. Any translated versions must be verified and approved by the IRB prior to their use.

Investigators conducting research in which it is anticipated that a non-English speaking population will be included should submit a foreign-language consent, as appropriate, at the time of initial submission.

L. Obtaining and Documenting Informed Consent of Subjects Who Are Illiterate

A person who can comprehend English but cannot speak or write can be enrolled into a research study if they are otherwise competent and able to communicate approval or disapproval. The

subject may be asked to "make his/her mark" on the consent form. The person shall be provided with a verbal explanation of the study, and the consent form shall be read to them and explained in detail. All of the other requirements of Informed Consent must be followed. The consent form should document the way in which information was conveyed to the subject, and the means by which the subject communicated agreement to participate in the study. An impartial third party must witness the entire consent process and sign the consent document.

CHAPTER 9

Special Populations and Special Studies

A. Research Involving Children

All research involving children shall be conducted and reviewed in compliance with the special DHHS requirements as set forth in 45 CFR 46 Subpart D, as well as State law governing such research.

Children are considered a vulnerable research population because their emotional and intellectual capacities may be limited and they are not of a legal age to give informed consent. The IRB is responsible for assuring that Principal Investigators/Project Directors conducting research with children comply with special requirements as set forth by the DHHS in 45 CFR 46 Subpart D. During its deliberations, the IRB will consider the degree of risk and potential benefit of the proposed activity and whether it is necessary to obtain the assent of the minor.

DEFINITIONS

Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research for the applicable state in which the research is being conducted.

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by applicable State law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage, or procreation.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care

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

Parent means a child's biological or adoptive parent.

Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

For submitting a protocol involving children:

The Principal Investigator must submit an assent from the subject (an assent form may be included as part of the consent form or be a separate document) in addition to all other required documents for protocol submission to the IRB. (See Asentral, Inc. IRB Study Application Form).

Permission by Parents or Guardians and Assent by Children

In addition, the IRB shall determine that adequate provisions are made for soliciting the assent of children, when in their judgment the children are capable of providing assent (generally children 7 – 9 years of age or older). To make this judgment, the IRB shall consider the ages, maturity, and psychological state of the subjects either as a group or for each child. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under the same circumstances in which consent may be waived.

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under Title 45 CFR 46.404 or 46.405. Where research is covered by Title 45 CFR 46.406 and 46.407 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.

If the research is designed for conditions or for a subject population for which parental/guardian permission is not a reasonable requirement to protect the subjects (i.e. neglected or abused

children), the IRB may waive the consent requirement but must provide an appropriate mechanism for protecting the children.

Individuals under the age of 18 who are considered emancipated minors by applicable state law may be able to consent to research participation for themselves. Although not specifically addressed by applicable state statute, there may be instances where participation in a clinical trial is the subject's only way to receive a particular form of treatment which may be beneficial. The IRB shall consider the inclusion of emancipated minors in research, absent parental or guardian consent, on a case-by-case basis. The IRB shall consider the subject's ability to comprehend what is being proposed, and the intervention or procedure involved in the research must offer a prospect of direct benefit that is important to the health or well-being of the minor and is not available outside the context of the research protocol.

Documentation of Permission and Assent

In cases where permission of a parent/guardian is required, it must be documented in accordance with informed consent requirements (see Informed Consent). For research where assent is also required, the IRB will determine whether and how it is to be documented. Generally, the use of an assent form is appropriate.

Children who are Wards

Children who are wards of the State or other agency, institution or entity, can be included in research under Title 45 CFR 46.406 or 46.407 only if such research is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institution, etc., in which the majority of the children involved are not wards.

For research approved by the IRB involving wards and within the categories listed above, the IRB shall require the appointment of an advocate for each child (in addition to the child's guardian), who has the experience to act in the best interests of the child and is not in any way associated with the research, investigator, or guardian organization.

B. Research Involving Pregnant Women, Human Fetuses, and Neonates

All research involving pregnant women, human fetuses and neonates shall be conducted and reviewed in compliance with the special DHHS requirements as set forth in Title 45 CFR 46 Subpart B.

DEFINITIONS

Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

Fetus means the product of conception from implantation until delivery.

Neonate means a newborn

Nonviable neonate means a neonate after delivery that, although living, is not viable.

Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:
(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy

resulted from rape or incest.
(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
(g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
(j) Individuals engaged in the research will have no part in determining the viability of a neonate

Research involving neonates.

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

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section 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 requirements of paragraph (b) or (c) of this section have been met as applicable.

(b)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 of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart 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 of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) 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 of this paragraph (c)(5), 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 of this paragraph (c)(5).

(d) 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 of this part.

Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) 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.
(b) If information associated with material described in paragraph (a) of this section 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 of this part 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.
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:
(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
(b) The Secretary, 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:

(1) That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or
(2) The following:

(i) 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;
(ii) The research will be conducted in accord with sound ethical principles; and
(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

PROCEDURE:

All Principal Investigators proposing such research activities will include, as part of their presentation to the IRB, assurances as to the following:

- Appropriate studies on animals and non-pregnant individuals have been completed;

- Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity;
- Individuals engaged in the activity will have no part in: (i) any decisions as to the timing, method and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy;
- No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity;
- No inducements, monetary or otherwise, may be offered to terminate pregnancy for the purposes of the activity

C. Research Involving Prisoners

All research involving prisoners shall be conducted and reviewed in compliance with the special DHHS requirements as set forth in 45 CFR 46 Subpart C.

The IRB is responsible for assuring that Principal Investigators/Project Directors conducting research with prisoners comply with special requirements as set forth in 45 CFR Subpart C. Inasmuch as prisoners may be under certain 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, additional safeguards exist in order to provide additional safeguards for prisoners involved in research activities.

DEFINITIONS

Prisoner means 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.

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.

Permitted Research Involving Prisoners

Biomedical or behavioral research involving prisoners as subjects may only be conducted if the IRB has approved the research under the guidelines as outlined above, and the Secretary, DHHS, determines that the proposed research involves solely the following:

- A 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 nor more than inconvenience to the subjects;

- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the research presents no more than minimal risk and no more than inconvenience to the subjects;

- 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 DHHS 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

- 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 has consulted with appropriate experts, including experts in penology, medicine and ethics, and published notice, in the **Federal Register**, of the intent to approve such research.

PROCEDURE:

When research involving prisoners is reviewed by the IRB, a consultant shall be called in to assist in the review of the protocol. This individual shall represent the prisoner population and shall be someone with appropriate background and experience to serve in that capacity.

The IRB shall consider the following in reviewing research involving prisoners

- The research must fall under one of the permissible categories as outlined below.

- Any possible advantages accruing to the prisoner through his/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/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;

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

- 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;

- The information is presented in language which is understandable to the subject population;

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

- 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.

D. Research Involving Incapacitated or Decisionally Impaired Subjects

NOTE: This does not apply to the category of research covered under the FDA's Guidelines for Emergency Research (see Emergency Use Exemption from Prospective IRB Approval).

Individuals with diminished autonomy deserve added protection in order to maintain their rights and welfare. For all research involving patients who lack capacity or decisionally-impaired subjects, the capacity of the potential research subject shall be assessed prior to their enrollment and then periodically throughout the course of the research; it will never be presumed that a patient's condition renders him/her incompetent. A legally authorized representative may consent to an individual's participation in research under the appropriate circumstances. Under limited circumstances, as determined by the IRB and based on risk, potential benefit, and the urgency of initiating treatment, approval for consent to be given by a surrogate such as next-of-kin may be granted for a protocol. Approval for the use of surrogate consent will be considered by the IRB for individual protocols in accordance with current Federal and State regulations and guidance.

Current Federal regulations do not specifically address the inclusion of decisionally impaired individuals in research. However, the NIH has issued guidance entitled Research Involving Individuals With Questionable Capacity to Consent: Points to Consider which can be very helpful in assessing this issue. The IRB shall act in accordance with current guidance when considering inclusion of vulnerable populations in research.

There are a number of situations where research subjects may be or may become unable to consent for their own participation in a research protocol. These guidelines include but are not necessarily limited to the following categories of studies:

- Psychiatric studies, where it is anticipated (but not presumed) that patients may be or become decisionally impaired
- Clinical protocols involving medical conditions which often (but not always) render a person physically unconscious or decisionally impaired (i.e. stroke, unstable or serious cardiac conditions, shock, mental status changes due to fever/infections or other reversible conditions, emergency, trauma and ICU research, drug abuse, etc.)
- All other research which may include subjects who might experience fluctuating decisional capacity (due to dementia, emotional distress, etc.)

DEFINITIONS

Cognitively Impaired: Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under

the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Competence: Technically, a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. (*See also: Incompetence, Incapacity*.) Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or incompetence pertains to an adjudication in court proceedings that a person's abilities are so diminished that his or her decisions or actions (*e.g.*, writing a will) should have no legal effect. Such adjudications are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations.

Incapacity: Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

Incompetence: Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

Institution: A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

PROCEDURE:

When an individual's capacity is in question, a psychiatrist and/or neurologist must assess the capacity of the prospective subject to consent and determine whether consent by a Legally Authorized Representative is appropriate or possible. The IRB may require that this assessment be done by a physician who is a third-party and who has no other involvement in the research. Federal Regulation allows for consent by a Legally Authorized Representative when a research subject is incompetent. For research purposes, a legally authorized representative is the parent or legal guardian of a minor, someone who is explicitly defined in a Health Care Proxy as being able to act on behalf of the individual, or someone who is court-appointed as such. Federal and State laws do not specifically state whether a next-of-kin may act as a Legally Authorized Representative in certain circumstances.

Where necessary, in order to screen subjects for sufficient comprehension and recall of information presented during the consent process, a two part consent process may be required by

the IRB, where the second part involves a test of the subject's comprehension and recall of the information presented in the first part. (e.g. for elderly subjects whose comprehension is questionable).

There are certain circumstances where it may be appropriate to allow a next-of-kin, who may not be a Legally Authorized Representative, to provide consent on behalf of an individual. The determination as to whether or not it is appropriate to accept consent by a next-of-kin is considered for individual protocols by the IRB, and is based on the risk/benefit ratio and the implications of delaying study participation for the amount of time it would take to appoint a legal guardian. The following categories defined for research involving children, defined in the Federal regulations in 45 CFR 46.404-407, are used as a guideline by the IRB in making this determination. However, under the Mental Hygiene regulations, siblings cannot consent for treatment.

46.404 Research <u>not</u> involving greater than minimal risk.

Consent should be sought from a Legally Authorized Representative, if reasonably available. If not, a family member, who is aware of the patient's values and believes the subject would have consented to participation may consent to their participation. The relationship between the subject and next-of-kin should be documented in the patient's research/medical record. (The following order should be used when seeking next-of-kin: Spouse, adult children, parents, adult siblings, grandparents, close friend.)

46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

A Legally Authorized Representative may consent on behalf of an individual for participation in this category of research. A request for approval of surrogate consent (i.e. consent by a family member who is not a Legally Authorized Representative) may be considered by the IRB if the research could not otherwise be carried out, and if exclusion of those individuals without a Legally Authorized Representative denies them access to a potentially beneficial treatment where no other comparable treatment is available, and there is genuine uncertainty about the effectiveness of standard care (i.e. there is clinical equipoise). This may include placebo-controlled trials. In order to protect the rights and welfare of the research participant, the use of a surrogate to consent on behalf of another individual in research involving greater than minimal risk will be determined for individual protocols by the IRB after careful consideration of the research protocol and in accordance with current Federal and State regulations.

The process for determining the appropriate surrogate should be carefully laid out by the Investigator for review by the IRB at the time of initial submission and, if granted, documented in the patient's medical/research record.

46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Only a legally authorized representative may consent on behalf of an individual for participation in this category of research.

46.407 Research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of humans

Requests under this category of research are extremely rare. Surrogate consent is never acceptable for participation in research falling under this category of research.

In addition to considering the risk/benefit ratio, the IRB will consider the following issues when making a determination regarding surrogate consent for a particular protocol in any/all categories of research:

- Will patient care be compromised by restricting participation to those with legally authorized representatives? (i.e. could a potentially beneficial treatment be denied to patients?)
- Will restricting the use of surrogates significantly affect study accrual for a beneficial study? (i.e. could the study practicably be carried out without the use of surrogates?)
- Is there time to go to court and appoint a guardian?

Assent of the Decisionally Impaired

The IRB may determine that the assent of the individual should be sought. For certain populations where the incapacity of the subject may be temporary, the IRB may determine that the consent from the individual is necessary to continue their participation in the study once capacity has been restored.

The IRB may require that a health care proxy be identified for future decision-making on behalf of a particular group of subjects whose capacity is expected to diminish over time. For instance, subjects who are asked to participate in a research study on Alzheimer's disease who are capable of consenting for themselves, but whose capacity is most likely to deteriorate during the course of the research, may be asked to assign a health care proxy for future decision making as a condition of being enrolled into the study.

All provisions for additional protections (e.g. assent, surrogate consent, capacity assessments, etc.) required by the IRB for the conduct of a particular protocol involving patients who lack capacity or decisionally impaired subjects will be outlined in the individual approval letters for each protocol.

E. Activities Involving Genetic Research or Tissue Banking

All research involving genetic research and tissue banking shall be given special consideration with regard to the unique risks presented by such research, and according to current regulation governing such research.

In genetic research and research using stored tissue samples there are potential health, societal, emotional and legal issues to consider. Many subjects may be naïve to these issues and it is therefore necessary for the IRB to evaluate the protocols and consent forms for such studies with great care. As this new science develops and laws evolve, it is important to continuously rethink and refine the issues and the way in which they are presented to subjects.

DEFINITIONS

Genetic tests: The analysis of human DNA, RNA, chromosomes, proteins or other gene products to detect disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.

Types of studies:

Prospective: studies in which the collection of the new samples is part of the study design.

Retrospective: Studies which utilize previously obtained samples collected for a purpose that is different from that of the current study.

Types of Samples:

Anonymous: Biological material that was originally collected without identifiers and is impossible to link to their sources.

Anonymized: Biological materials that were initially identified, but have been irreversibly stripped of all identifiers and are impossible to link to their sources. (This process does not preclude linkage with clinical, pathological and demographic information before the subject identifiers are removed. Caution must be exercised so that the amount and type of linked information does not invalidate anonymity.)

Identifiable: Biological materials that are unidentified for research purposes, but can be linked to their sources through the use of a code. Decoding can only be done by the investigator, or another member of the research team.

Identified: Biological material to which identifiers, such as name, patient number, or clear pedigree location, are attached and available to the researchers.

Research using Prospectively Collected Samples

In prospective research, the investigators have the responsibility to communicate with the potential subject and obtain informed consent. Additionally the investigator has the obligation to maintain confidentiality to the extent permitted by law. (This is necessary unless the samples are collected **anonymously**.)

The consent forms for such research should clearly indicate what information could result from the research, what the implications and limitations are, that unexpected findings may result, and what follow-up information subjects will receive (if any, as many studies are preliminary and results may not be meaningful or validated). If results are to be given, subjects should be offered counseling, as appropriate, since results from such research could lead to adverse psychological outcomes, social stigmatization and discrimination. In certain cases subjects should be given the option to determine whether they want to be informed of the results of their testing. The disposition of their samples should be included in the consent process and form; if samples are to be stored for future studies, subjects need to be informed of how long storage will continue and the possibility of storage failure.

Retrospective Studies of Existing Samples

When retrospective research is done using **anonymous** or **anonymized** samples, consent from subjects may not be necessary, since the subjects cannot be individually identified and there is no expected risk to the subject. For research using samples that are identifiable, consent must be obtained. In certain cases the investigator may seek a waiver as detailed in 45 CFR 46.116 (see section on Informed Consent).

See Guidelines for Preparing Research Consent Forms: Required and Suggested Language, for a description of sample consent language pertaining to genetic research and tissue banking.

F. Additional Special Classes of Subjects

In addition to the vulnerable populations discussed separately (Children, Fetuses/Pregnant Women/Human *in vitro* Fertilization, Prisoners, Incompetent/Decisionally Impaired), the IRB shall provide additional protection to other potentially vulnerable populations. This special class of subjects may include, but is not limited to, terminally ill patients, elderly/aged persons, minorities, student/employees/normal volunteers, economically or educationally disadvantaged persons, and international research participants.

Terminally Ill Patients

Terminally ill patients are those who are deteriorating from a life-threatening disease or condition for which no effective standard treatment exists. It is generally considered unacceptable to ask such persons to participate in research for which alternative, not similarly burdened, populations of subjects exist. Nevertheless, it may often be necessary to involve

terminally ill patients in research concerning their disease and its treatment. Further, terminally ill persons should not be excluded from research in which they may want to participate simply because of their status. One can imagine that altruism and a desire to bring good from adversity may well motivate persons suffering from life-threatening illnesses to become involved in biomedical or behavioral research. Still, terminally ill individuals are a vulnerable population of research subjects, and therefore, require additional protection against coercion and undue influence [45 CFR 46.111(b)].

The FDA has a program of Expanded Access that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them (e.g. Treatment INDs, Parallel Track).

In many contexts, research on terminal illness and its treatment requires the involvement of terminally ill patients when alternative populations for study do not exist or when involving alternative populations would be ethically unjustifiable. Two important reasons for concern regarding research involving terminally ill persons are: (1) they tend to be more vulnerable to coercion or undue influence than healthy adult research subjects; and (2) research involving the terminally ill is likely to present more than minimal risk.

The risk of coercion and undue influence may be caused by a variety of factors. In addition to the fact that severe illness often affects a person's competence (see Research Involving Incapacitated or Decisionally Impaired Subjects), terminally ill patients may be vulnerable to coercion or undue influence because of a real or perceived belief that participation is necessary to receive continuing care from health professionals or because the receipt of any treatment is perceived as preferable to receiving no treatment. Although terminally ill patients should be protected from an understandable tendency to enroll in research under false hopes, IRBs should not take too protective an attitude toward competent patients simply because they are terminally ill. Some terminally ill patients may find participation in research a satisfying way of imparting some good to others out of their own misfortune.

It is important to distinguish between risks that may be justified by anticipated benefits for the research subjects and risks associated with procedures performed purely for research purposes. A particularly difficult issue relating to research involving terminally ill patients arises in connection with the conduct of Phase I drug trials in which the drugs involved are known to be particularly toxic (e.g., a new form of cancer chemotherapy). In some of these studies, any benefit to the subject is, at best, highly unlikely. Despite the "therapeutic intent" (the research physician's intent to provide some benefit to improving the subject's condition) of the investigators to benefit the subject, subjects may in fact experience a decline in health status, no improvements in terms of quality of life, or lengthened life for only a short time. It is extremely important that prospective subjects be clearly informed of the nature and likelihood of the risks and benefits associated with this kind of research. The challenge to the investigator and the IRB is to provide patients with an accurate description of the potential benefits without engendering false hope.

Elderly/Aged Persons

As the American population ages, research on the aging process and conditions and diseases that disproportionately affect the elderly has become increasingly important. The participation of older subjects in research poses several issues for IRBs; primary among them is the question of whether and when the elderly need special protections. IRBs must maintain the balance between the need for protection and the need to provide respect for persons.

While the federal regulations call for additional protections for vulnerable populations, there are no specific regulations governing research with elderly subjects. It is generally agreed, however, that the elderly are, as a group, heterogeneous and not usually in need of special protections, except in two circumstances: cognitive impairment and institutionalization. Under those conditions, the same considerations are applicable as with any other, non-elderly subject in the same circumstances (see The Research Involving Incapacitated or Decisionally Impaired Subjects).

There is no age at which prospective subjects should become ineligible to participate in research. Most older people are neither cognitively impaired nor live in institutional settings. Nevertheless, investigators may avoid elderly subjects because of recruiting/retention difficulty, hearing/vision impairment (making the consent process more difficult), memory impairment, etc. However, inclusion of older persons in research is important, and they should have the opportunity to share in the benefits of burdens of research.

In the past, persons in nursing homes or other institutions have been selected as subjects because of their easy accessibility. It is now recognized, however, that conditions in institutional settings increase the chances for coercion and undue influence because of the lack of freedom inherent in such situations. Research in these settings should therefore be avoided, unless the involvement of the institutional population is necessary to the conduct of the research (e.g. the disease or condition is endemic to the institutional setting itself).

Minorities

The inclusion of minorities in research is important, both to ensure that they receive an equal share of the benefits of research and to ensure that they do not bear a disproportionate burden. Most diseases affect all population groups, minority and non-minority alike. For generalizability purposes, investigators must include the widest possible range of population groups. Sometimes, however, minorities are subject to a differential risk. Some research, for example, relates to conditions that specifically affect various minority groups (e.g., sickle cell anemia or Tay Sachs disease), so that involvement of the relevant minority groups is imperative. Other research focuses on characteristics of diseases or effectiveness of therapies in particular populations (e.g., HIV transmission, treatment for hypertension), and may also concern conditions or disorders that disproportionately affect certain racial or ethnic groups. Exclusion or inappropriate representation of these groups, by design or inadvertence, would be unjust. Further, to the extent that participation in research offers direct benefits to the subjects (in HIV research, for example,

the receipt of a promising new drug), under-representation of minorities denies them, in a systematic way, the opportunity to benefit. A glaring example of abuse of minority populations' bearing the burden of research can be found in the Tuskegee study, in which a group of African-American men suffering from syphilis were left untreated, despite the availability of penicillin, in order to study the natural course of the disease.

The manner in which subjects are selected bears directly on the problem of inclusion of minorities. The choice of a geographic area for recruitment may affect the representation of racial and ethnic groups in study populations. Also, to the extent that minorities are reliant on public rather than private health care systems, recruitment of subjects from private physicians will tend to exclude minorities and recruitment from public health clinics will tend to over include them. In fact, recruiting subjects from any health care system assumes that appropriate subjects have access to and exercise their ability to access a health care system, which may contribute to the homogeneity of the study population. Some writers have suggested that investigators change recruitment strategies so that they recruit subjects through community-based institutions such as churches and neighborhood organizations, rather than solely through health care institutions. In many studies, several institutions collaborate, thereby enrolling subjects from different geographic locations. Such collaborations may also provide a mechanism for ensuring appropriate representation of women and minorities in the study population.
One justification that is offered for research with homogeneous populations is that it is a simpler, less costly way to conduct clinical trials. The more diverse the study population, the larger the subject pool must be (to achieve statistical significance when controlling for differences in race, gender, and ethnicity) and the more variables must be accounted for in analyzing the data. Nonetheless, when homogeneous populations are used, study results are then limited in their applicability to the precise population involved in the study, and may, in fact, hide inaccuracies.

Students, Employees and Normal Volunteers

Normal Volunteers. Strange as it may seem at first, special concerns surround the involvement of normal (i.e., healthy) persons who volunteer to participate in research. Primarily, the principles involved are **beneficence** and **respect for persons**. In the Belmont Report, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research stated the two general rules that describe beneficent actions as: (1) do not harm; and (2) maximize possible benefits and minimize possible harms. Volunteers for whom no therapeutic benefit can result from participation in research should, therefore, be exposed to risks that are minimized to the greatest extent possible. While the minimization of risks is an important requisite for any research involving human participants, the altruistic motivation of the normal volunteer's agreement to participate (i.e., of contributing to scientific knowledge for the benefit of society) heightens the concern for the risks to which such participants should ethically be exposed.

The principle of **respect for persons** requires that research participants are, where capable of doing so, allowed to act autonomously and to express their right of self-determination. These principles are effectuated through the process of informed consent, which involves providing

subjects with all relevant information about the study, including the risks and benefits involved, in clear and simple language, and ensuring that the information is understood and appreciated. Furthermore, the agreement to participate must be **voluntary**; the consent negotiations must be free from elements of coercion or undue inducement to participate. In research involving normal volunteers, particularly where the research involves more than **minimal risk**, IRBs must ensure that any monetary payments to subjects are not so great as to constitute an undue inducement. This issue may be particularly difficult for IRBs to deal with. Since subjects who volunteer to participate in such studies are usually compensated for their time and discomfort, IRBs should seriously scrutinize the payment schedules to ensure that any compensation offered is commensurate with the time, discomfort, and risk involved. Even so, where a research procedure involves serious discomfort and/or the real, though slight, possibility of serious harm (e.g., studies that involve the insertion and positioning of catheters in veins or the heart), one can easily imagine that the motivation of persons who volunteer to participate may be monetary. IRBs should pay particular attention to the proposed study population and whether it may comprise persons who are likely to be vulnerable to coercion or undue influence, such as persons who are educationally or economically disadvantaged. The federal regulations require that IRBs employ special safeguards under such circumstances [45 CFR 46.111(b)].

One area where normal volunteers are employed in research is in Phase 1 drug trials. The justification for the involvement of normal, healthy subjects is the need for volunteers whose experience with the trial materials is more easily analyzed because of the existence of fewer confounding factors. While Phase 1 trials are the first use of experimental drugs and devices in humans, preliminary studies involving animals provide investigators with data indicating a high likelihood of safe use in humans. Studies have indicated that the risk of injury from participating in Phase 1 studies is small, about the same as the risk of being injured while working as an office secretary [Levine (1982)]. The likelihood of risk, including the availability of animal data, should be scrutinized by IRBs.

Normal volunteers, like students and employees, should be recruited through general announcements or advertisements, rather than through individual solicitations. Personal solicitations increase the likelihood that participation will be the result of undue influence, either because of the relationship between the recruiter and the prospective subject, or methods of communication employed by the recruiter that may act to persuade prospective subjects to participate, thus compromising the voluntary nature of the agreement to participate.

Investigators and IRBs should carefully consider what will happen if and when a normal volunteer should become sick or be injured during the research. As with any research involving human subjects, such issues should be clearly spelled out in the informed consent document, and should be reviewed carefully with the prospective subject. For example, subjects should be told: whether any medical treatments will be made available should injury occur and, if so, what they consist of; whom to contact should a research-related injury occur; and that they may discontinue participation at any time without penalty or loss of benefits to which they would otherwise be entitled [45 CFR 46.116(a)(6-8)]. In addition, where appropriate subjects should be told whether they will be dropped from the study in the event of injury or illness, and whether they will be

required to pay for treatment of research-related injuries or illness [45 CFR 46(b)(2-3)]. Where illness in healthy volunteers does occur, particularly during a drug study, investigation by an independent physician may be warranted. [See Fazackerley, Randall, and Pleuvry (1987).] The issues raised by the involvement of healthy subjects in genetic research is discussed in Guidebook Chapter 5, Section H, "Human Genetic Research."

Students. Universities, and the association of investigators with them, provide investigators with a ready pool of research subjects: students. Many IRBs have faced the question of whether and in what way students may participate in research. Two questions that have been posed are whether students - medical students, in particular - should be allowed to participate in biomedical research (and whether special protections should be adopted to restrict their participation), and whether participation in research can appropriately be included as a course component for course credit. The latter practice is commonly employed in psychology departments.

The problem with student participation in research conducted at the university is the possibility that their agreement to participate will not be freely given. Students may volunteer to participate out of a belief that doing so will place them in good favor with faculty (e.g., that participating will result in receiving better grades, recommendations, employment, or the like), or that failure to participate will negatively affect their relationship with the investigator or faculty generally (i.e., by seeming "uncooperative," not part of the scientific community). Prohibiting all student participation in research, however, may be an over protective reaction. An alternative way to protect against coercion is to require that faculty-investigators advertise for subjects generally (e.g., through notices posted in the school or department) rather than recruit individual students directly. As with any research involving a potentially vulnerable subject population, IRBs should pay special attention to the potential for coercion or undue influence and consider ways in which the possibility of exploitation can be reduced or eliminated.

Whether medical students in particular require special protections has been hotly debated. Some universities have either prohibited their participation or severely restricted it to, for instance, research involving minimal risk and minimal interruption of time. Strong arguments have been made against such protections, including claims that as future physicians (and possibly researchers) they may be obliged to participate. Angoff has argued that protecting medical students to a greater degree than protecting other normal volunteers smacks of elitism. Angoff (1985) states, "One may wonder why it is acceptable to ask the masses to accept risk in the name of science but not the very people whose futures are linked to the successful perpetuation of biomedical research" [p. 10]. Nolan (1979), Levine (1984), Angoff (1985), and others have argued that medical students are in a particularly good position to participate in some biomedical research because of their ability to comprehend the procedures involved in studies and evaluate the risks involved, which may not be possible to achieve with other normal volunteers. Angoff and others have also argued that it is acceptable to pay medical students as one would any research participant.

Requiring participation in research for course credit (or extra credit) is also controversial, though common in the social and behavioral sciences. The justification offered for requiring student

participation is educational benefit [Gamble (1982); Cohen (1982)]. Clearly, however, participation of students is seen by faculty-investigators as necessary to the conduct of their research. Grant budgets often do not allow investigators to pay subjects; giving course credit or extra credit is a means of obtaining sufficient participation rates. Again, the issue for IRBs is whether such arrangements for selecting subjects are fair and non-coercive.

Participation in studies might be mandatory or for extra credit. Students in beginning psychology courses, for instance, might be required to serve as subjects for a given number of hours of research or in a given number of research projects. Or they might be given the option of participating for additional grade credit. Several mechanisms have been suggested for diminishing or eliminating the coercive aspect of student participation for course credit that IRBs might find useful. Gamble (1982) describes a departmental guideline for research involving students where extra credit is offered for participation. Students are to be given other options for fulfilling the research component that were comparable in terms of time, effort, and educational benefit: "for example, short papers, special projects, book reports, and brief quizzes on additional readings" [p. 7]. He raises concerns about the comparability of such alternatives with participating in research (e.g., that if they participate in studies, all they have to do is show up and spend the time, but if they choose to write a paper, it gets graded, and if they do extra readings, they have to be tested on them), and concludes that paying student subjects as researchers would any other subject is the only way to protect students' freedom of choice to participate. Cohen (1982) describes a similar policy that seems to meet these concerns. To fulfill the research component, students can either participate in five hours of research, write a brief research paper, or attend faculty research colloquia. The paper is not graded, and students who attend the colloquia have only to show up. If students do choose to participate in studies, the policy seeks to increase the likelihood that participation is freely chosen by requiring: that students be given several studies to choose from and may not be required to volunteer for any particular study; that the studies must not involve more than minimal risk; that students can withdraw from the study at any time without losing the extra credit [p. 11].

Another concern raised by the involvement of students as subjects is confidentiality. As with research involving human subjects generally, IRBs should be aware that research involving the collection of data on sensitive subjects such as mental health, sexual activity, or the use of illicit drugs or alcohol presents risks to subjects of which they should be made aware and from which they should be protected, to the greatest extent possible. The close environment of the university amplifies this problem.

Where students are likely to be participating in research, IRBs should consider including a student member or consulting with students where appropriate.

Employees. The issues with respect to employees as research subjects are essentially identical to those involving students as research subjects: coercion or undue influence, and confidentiality. As medical students have seemed ideal subjects by biomedical researchers, employees of drug companies have been seen by investigators as ideal subjects in some ways, because of their ability to comprehend the protocol and to understand the importance of the research and compliance with the protocol

G. Medical Devices

Investigators pursuing the use of an investigational device, the investigational use of an approved device, or the humanitarian use of a device (HUD), as defined in this policy, must obtain IRB approval for its use prior to implementation.

A medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis (IVD) of disease and other medical conditions such as pregnancy. Clinical investigations of medical devices must comply with the Food and Drug Administration (FDA) informed consent and Institutional Review Board (IRB) regulations [21 CFR parts 50 and 56, respectively]. Federal requirements governing investigations involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990.

510(k) devices

FDA reviews pre-market 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 premarket 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 premarket approval before it can be marketed unless it is reclassified into a lower regulatory class.

Investigational Device Exemption (IDE)

The IRB shall make a determination as to whether the device can be classified as SR or NSR. The IRB shall then consider whether or not the study should be approved. In considering whether a study should be approved, the IRB shall 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 [21 CFR 56.110]. FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB should consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures.

Frequently Asked Questions About IRB Review Of Medical Devices
(FDA Information Sheets)

1. What is meant by Class I, II and III devices?

The class distinction is made primarily on the level of risk to users/patients and, therefore, the level of FDA oversight needed to ensure that the device is safe and effective as labeled. Generally, but not always, this corresponds to logical risk evaluations.

Class I:	General controls	crutches, band aids
Class II:	Special controls	wheelchairs, tampons
Class III:	PreMarket Approval	heart valves (known to present hazards requiring clinical demonstration of safety and effectiveness) - OR - not enough known about safety or effectiveness to assign to Class I or II

2. What is the difference between marketing approval under a 510(k) and under a PMA?

A 510(k) application demonstrates that a new device is substantially equivalent to another device that is legally on the market without a PMA. If FDA agrees that the new device is substantially equivalent, it can be marketed. Clinical data are not required in most 510(k) applications; however if clinical data are necessary to demonstrate substantial equivalence, the clinical studies need to be conducted in compliance with the requirements of the IDE regulations, IRB review and informed consent (21 CFR parts 812, 56 and 50, respectively).

3. Why should an IRB decide whether a device is non-significant risk (NSR)?

The sponsors (usually the manufacturer of the device) make the initial decision whether a device imparts significant risk (SR) to study subjects or others. If so, the sponsor obtains an Investigational Device Exemption (IDE) from FDA. If the sponsor believes the device does not impart significant risk, IRB approval of a study as an NSR device can be sought. The NSR category was created to avoid delay and expense where the anticipated risk to human subjects did not justify the involvement of FDA. If the IRB agrees that the study is NSR, no submission to or review by FDA is necessary before starting studies in humans. If the IRB considers the study to be SR, the sponsor must obtain an IDE from FDA before proceeding with clinical studies.

4. What does FDA know about an NSR study?

"There is no requirement to report to FDA when an NSR study starts." The requirements for IRB review, informed consent, adverse event reporting and labeling still apply. In addition, the sponsor should understand that proceeding with an NSR study is at their risk (meaning that the FDA can later disagree) and they may voluntarily seek advice or inform FDA about the decision to proceed without filing an IDE with FDA.

5. How does an IRB decide whether a device is SR or NSR?

The IRB uses its best abilities, the information in the regulations and the guidelines, and the risk evaluation provided by the applicant. It can, as always, seek outside assistance. The IRB should have written policies and procedures regarding device review. The information sheet "Significant Risk and Non-Significant Risk Medical Device Studies" provides additional guidance.

6. Does an IRB that reviews medical device studies need written procedures for determining whether the device is SR or NSR?

When the IRB determines that an investigation presented for approval as involving an NSR device actually involves an SR device, 21 CFR 812.66 requires the IRB to so notify the investigator and, where appropriate, the sponsor. 21 CFR 56.108(a)(1) requires the IRB to follow written procedures for conducting its initial review of research and for reporting its findings and actions to the investigator. The procedures followed in determining whether a study is SR or NSR should be included among those written procedures.

7. Does FDA require IRB review of the off-label use of a marketed device?

YES, if the off-label use is part of a research project involving human subjects. NO, if the off-label use is intended to be solely the practice of medicine, i.e., for a physician treating a patient and no research is being done.

8. What is the meaning of exemption in 21 CFR 812.2(c)(2)?

The exemption applies only to investigations in which 510(k)'d products are being used in accordance with the labeling cleared by FDA. Investigation of an off-label use of a 510(k) product takes it outside this exemption. A device subject to 510(k) remains "investigational" until the 510(k) is cleared by FDA and the investigational use is subject to the requirements of the IDE regulation, informed consent and IRB review (21 CFR 812, 50 and 56, respectively).

9. Must an IRB review a clinical investigation being done after submission of a 510(k)?

YES, if it's research the 21 CFR 50 and 56 regulations apply, and an IRB should review it. A 510(k) allows commercial distribution; it doesn't address research use. A 510(k) application can take time to process during which it remains an investigational product. It cannot be distributed except for investigational use until FDA clears the 510(k) application.

Also see FDA Information Sheets: "Medical Devices," "Significant Risk and Non-significant Risk Medical Device Studies" and "Emergency Use of Unapproved Medical Devices."

Chapter 10

Conflicts of Interest and Complaint Reporting

A. Conflict of Interest

- In order to comply with the Department of Health and Human Services (DHHS) guidance entitled "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," we have established a policy for reviewing financial conflicts of interest of investigators, research staff and institutions. There is a section of the Asentral, Inc. IRB Study Application Form dedicated to reporting of financial conflicts of interest.

  The investigator or study staff will be considered to have a financial conflict of interest if they or their immediate family have material interests over $10,000 in the sponsoring entity, including speaking fees, consultation fees, stock ownership or other equity interests, patents, trademarks, copyrights, or licensing agreements. Interests under $10,000 are not considered to present a financial conflict, unless such interests represent over 5% ownership in the sponsoring entity.

Significant financial interest means:

A financial interest consisting of one or more of the following interests of the Researcher (and those of the Researcher's spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:

- With regard to any publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the 12 months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. (For purposes of this definition, remuneration includes salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest as determined through reference to pubic prices or other measures of fair market value);

- With regard to any non-publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the 12 months preceding the disclosure, when aggregated, exceeds $5,000 or when the Investigator (or the Investigator's spouse or dependent children) holds any equity interest (e.g., stock, stock option, or other ownership interest); or
- Intellectual property rights and interest (e.g. patents, copyrights), upon receipt of income related to such rights and interests;
- Investigators must also disclose the occurrence of any reimbursed or sponsored travel (i.e., that which is paid on behalf of the Investigator and not reimbursed to the Investigator so that the exact monetary value might not be readily available) related to the institutional responsibilities; provided, however, that this disclosure does not apply to travel that is reimbursed or sponsored by a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C.1001(a), an academic teaching hospital, or a research institute that is affiliated with an institution of higher education.

Possible Board Actions:
The following are actions the Board may take regarding conflicts of interest:

- A finding that the conflict of interest is not likely to jeopardize subject safety or bias the investigator's decision-making and does not require further action.
- A finding that disclosure of the conflict to subjects or others is unnecessary.
- A finding that controls on the conflict need to be put into place, such as limiting the role of the investigator with a conflict of interest.
- A finding that the conflict is unacceptable, and must be eliminated in order for the research to proceed.

4.6 Payment to Research Subjects

Any payment or gift to research subjects shall not be of such an amount as to be coercive to present undue influence on the potential subject's decision to participate in the research.

GUIDANCE:

The FDA provides the following guidance with regard to payment to research subjects, and shall be used by the IRB in reviewing protocols which involve payment to research subjects as a recruitment incentive for potential participants [http://www.fda.gov/oc/ohrt/irbs/toc4.html#payment]:

"It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and

timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time that they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

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 to FDA, providing that such incentive is not coercive. The IRB should 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."

B. Reviewing and Processing Complaints/Concerns, Questions on Subject's Research Rights, or Suggestions/Input

The right of research subjects to complain, voice a concern, or ask a question about a research study and to have the complaint, concern or question should be resolved in a timely manner. Complaints/Concerns/Questions may be raised by research subjects (past, present and potential), family members, designated spokespersons or anyone and provided to the IRB by phone, in writing, or in person.

Complaints or concerns can be submitted to the IRB by conventional mail, e-mail, FAX, telephone, or via the Sentry on the Asentral, Inc. IRB website.

Procedure:

1. Principal Investigator Responsibilities:

a) The Principal Investigator will address complaints/concerns/questions received from subjects or others as quickly as possible.

(i). If the complaint/concern of a subject or others indicates an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern cannot be resolved by the Principal Investigator, it must be reported as an unanticipated event involving risks to subjects or others up within 10 working days.

(ii). If the complaint/concern does not indicate an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern can be resolved by

the Principal Investigator, the information associated with the complaint/concern will be included as part of the continuing review submission for review by the IRB.

b) The Principal Investigator is responsible for ensuring the IRB-approved consent documents contain accurate information for contacting the Principal investigator should the subject have questions or research-related problems and contact information for the IRB should the subject have questions about the subject's rights as a research subject or to report research-related problems.

2. The IRB Administrator Responsibilities:

The AIRB Administrator (who is also the AIRB Human Research Protection Program Director) is responsible for initial review of the complaint/concern/question and communicating with the person who has the complaint/ concern/question.

a) The IRB Administrator will obtain and document the following information, as appropriate:
   i. The person's name and contact information (address, phone number, email address). Collection of this information is not mandatory. However, if the person wishes to remain anonymous, the person will be advised that a thorough review may not be possible and that without this information, follow-up with the person would not be feasible).
   ii. The study number and name of the Principal Investigator.
   iii. The person's relationship to the study such as past participant, present participant, potential participant, participant family member, etc.).
   iv. A detailed explanation of the complaint/concern/question.
   v. Who the person has contacted regarding the complaint/concern/question such as the principal investigator, research staff or anyone else and when such contact was made.
   vi. A description from the person of a proposed resolution of the complaint/concern, if the person has such a proposal.

b) The IRB Administrator will communicate to the person that he/she will inquire into the circumstances associated with the complaint/concern/question and that a response regarding the resolution of or a determination about the complaint/concern/question will be provided to the person along with an approximate estimate of when the response will be provided. The Director will also inform the person about the limits of confidentiality in regards to the inquiry including who may be informed, what information may be reviewed, etc.

c) The IRB Administrator will review study documents and other relevant information to begin the initial review of the complaint/concern/question. The Administrator may also contact the Principal Investigator, either verbally or in writing, to obtain information in association with the initial review.

d) After performing the initial review, the Administrator will determine whether the complaint/concern/question is minor and can be handled administratively or whether the complaint/concern/question needs to be reviewed by the IRB Chair and/or the IRB.
   i. If the complaint/concern/question is determined to be minor including those that do not involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study such as the subject not receiving approved compensation for participation, the review and response for such

complaints/concerns/questions may be done at the administrative level by the HRPP Director. The written report associated with the complaint/concern/question and response including corrective action will be made a part of the project file and need not be provided to the appropriate IRB Chair for review.

ii. If the complaint/concern/question is determined to involve potential risk to the subjects or others or cause a change in the risk/benefit ratio associated with the study, the written report will be provided to the IRB Chair for review.

iii. If the complaint/concern/question is determined to be an allegation of noncompliance, the IRB has the authority to suspend or terminate protocols that are found to be noncompliant with the IRB policies and procedures, state laws, and/or federal laws or regulations or have been associated with unexpected serious harm to subjects.

3. IRB Chair / IRB Review Procedures:

After the IRB Administrator has provided the report and response regarding the complaint/concern/question to the IRB Chair, the IRB Chair will do the following:

a) If the IRB Chair determines that the complaint/concern/question does not involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study, the Chair may accept the report and provide to the AIRB Administrator written acceptance of the report. The report and acceptance of the report will be made a part that particular study file.
b) If the IRB Chair determines that the complaint/concern/question involves potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study, the IRB Chair may determine the complaint/concern/question requires review by the full Committee and will return the report and response to the HRPP Director so the report and response may be placed on the next appropriate meeting agenda for IRB review.
c) If the IRB Chair determines that the complaint/concern/question would have an immediate effect to the health, welfare and/or rights of subjects, the IRB Chair will contact the Principal Investigator of the study to establish procedures for the protection of subjects pending review by the IRB.
d) If the complaint/concern/question is reported to the IRB by the Principal Investigator, the complaint/concern/question will be reviewed as a continuing review; report of serious adverse events, major protocol deviations/violations, or unanticipated problems; or other event.
e) If the IRB determines that the complaint/concern/question is an unanticipated problem(s) involving risks to others; serious or continuing noncompliance; or a violation that results in suspension or termination of IRB approval, the determination and appropriate information must be reported to the appropriate federal agencies.
f) The PI will be informed in writing of the results of the review of the complaint/concern/question by IRB within 10 working days.

Food and Drug Administration (www.fda.gov)

This website includes valuable information related to products regulated by the FDA, including links to CBER (Biologics), CDER (Drugs), and Device Advice (Devices)

Office for Human Research Protections (http://ohrp.osophs.dhhs.gov)

OHRP is the federal office responsible for the oversight of all of the human subjects research approved by one of our IRBs. This site contains a number of links to educational materials, regulations, guidance, decision letters, etc.

National Institutes of Health (www.nih.gov)

Source Documents

Belmont Report (http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm)
Nuremberg Code (http://ohsr.od.nih.gov/nuremberg.php3)
Declaration of Helsinki (http://www.wma.net/e/policy/17-c_e.html)
IRB Guidebook (http://ohrp.osophs.dhhs.gov/irb/irb_guidebook.htm)

Organizations/Agencies

ARENA (Applied Research Ethics National Association) –
www.primr.org/arena.html

PRIM&R (Public Responsibility in Medicine and Research) –
www.primr.org

The President's Council on Bioethics –
http://www.bioethics.gov/

ORI (Office of Research Integrity) –
http://ori.dhhs.gov

CIOMS (Council for International Organizations if Medical Sciences) –
http://www.cioms.ch/

Centers for Medicare and Medicaid Services (formerly HCFA) –
http://www.hcfa.gov/

HIPAA –
http://www.hcfa.gov/hipaa/hipaahm.htm

Regulations

45 CFR 46 (Common Rule) –
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

OHRP Guidance Documents –
http://ohrp.osophs.dhhs.gov/g-topics.htm

21 CFR 50 (Protection of Human Subjects) –
www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html

21 CFR 54 (Financial Disclosure by Clinical Investigators) –
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart

21 CFR 56 (Institutional Review Boards) –
http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr56_00.html

21 CFR 812 (Investigational Device Exemptions) –
www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html

International Conference on Harmonisation (ICH) –
http://www.ifpma.org/ich1.html

Good Clinical Practice in FDA Regulated Clinical Trials -
http://www.fda.gov/oc/gcp/default.htm

Other Interesting and/or Useful Sites

Online Medical Dictionary –
http://www.graylab.ac.uk/omd/index.html