Part 1 The Institutional Review Board for the Protection of Human Subjects

Part 2 Responsibilities of Researchers

Part 3 Informed Consent

Part 4 Additional Safeguards

Part 5 Investigational New Drugs and Investigational Devices

Part 6 Special Research Domains

OAKLAND UNIVERSITY GUIDELINES FOR RESEARCH INVOLVING HUMAN SUBJECTS

Part 1 The Institutional Review Board for the Protection of Human Subjects (IRB)

Oakland University is subject to federal guidelines for the protection of human subjects in research: Title 45, Code of Federal Regulations, part 46 (abbreviated as 45 CFR 46) www.gpoaccess.gov/cfr/retrieve.html (refer to 45 CFR 46, subparts a, b, c, d). The Food and Drug Administration (FDA) www.**fda**.gov, and the Office for Human Research Protections (OHRP) www.hhs.gov/**ohrp**, located within the Department of Health and Human Services (DHHS) are the primary regulating agencies for approval of research using human subjects or human materials. Much of the information found in these Guidelines is also available in the Institutional Review Board Guidebook, published electronically by OHRP at: www.hhs.gov/**ohrp**. As required by law, Oakland University has filed a Federal-wide Assurance of compliance with OHRP, and this assurance must be renewed every three years. The Assurance is a contract between Oakland University and OHRP, on behalf of the Secretary of Health and Human Services, stipulating the methods by which Oakland University will protect the welfare of research subjects in accordance with the federal regulations.

Oakland University is committed to the highest ethical standards of human subjects research as required by local, state, and federal laws and the ethical principles set down in the Belmont Report **http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm**, the Declaration of Helsinki **http://www1.va.gov/oro/apps/compendium/Files/helsinki89.htm** and the Nuremberg Code **http://www.hhs.gov/ohrp/references/nurcode.htm**. All research involving the participation of human subjects or their private records, regardless of funding, must be submitted to the Institutional Review Board (IRB) for review before research may begin.

Research must meet the definition of "research" and "human subject" to be considered for review by the Oakland University IRB. The Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) define these terms as follows.

Under the **DHHS** regulations, "research" means a systematic investigation, including development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

The **DHHS** defines "human subject" as a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual or identifiable private information.

Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Identifiable private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Under the **FDA** regulations, research is a clinical investigation and is defined as any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Food, Drugs, and Cosmetics Act, or need not meet the requirements for prior submission to the FDA under these sections of the Food, Drug, and Cosmetics Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

The **FDA** definition of human subject is an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy individual or a patient. For research involving medical devices, a human subject is also an individual on whose specimen an investigational device is used. Test article means any drug for human use, biological product for human

use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

An initial determination of whether or not a proposed activity should be considered "human subjects research" under the federal definition should be submitted to the IRB for a determination since this decision has important ramifications for Oakland University. A failure to submit a human subjects research project to the IRB for review violates assurances made to the federal government by the university and can result in severe financial penalties and other sanctions to the university. This decision has ramifications for faculty as well, and a failure to comply can be considered academic misconduct by the investigator(s).

Section 1.1 Activities Requiring Review and Approval by the IRB

(a) As mandated by the Code of Federal Regulations (45 CFR 46) and the Federal-wide Assurance, all research protocols involving human subjects, their private records, coded private information, or biological specimens must be approved by the Oakland University Institutional Review Board (IRB) prior to the research being conducted. The type of IRB review required depends on the level of risk to subjects as defined in 45 CFR 46. The IRB must review and approve all research involving human subjects if one or more of the following apply:

(1) The research is sponsored by Oakland University, regardless of the location of the project.

(2) The research is conducted by, or under the direction of, any staff, faculty, student, or other agent of Oakland University.

(3) The research is conducted using any Oakland University property or facility.

(4) Oakland University is "engaged" in the research.

(5) The research involves the use of Oakland University's non-public information to identify or contact human research subjects or prospective subjects.

(b) An exception to mandatory review and approval by the Oakland University IRB is the case of research conducted on hospital premises by faculty with dual appointment status at Oakland University and an area hospital with an accredited IRB. Oakland faculty with such dual appointments who are engaged in hospital research activities that are funded by grants in which Oakland University is not a signatory participant, are not required to submit an application for a research project to the Oakland University IRB. Instead, a copy of the funded proposal (including a copy of the hospital IRB approval) must be sent to the Office of Research Administration, to be kept on file.

(c) Oakland University faculty and students without dual appointments may also conduct research in collaboration with faculty at other institutions. Dual IRB approval is not required in these cases provided that the collaborating institution (s) has entered into an IRB authorization agreement establishing the lead institution and the IRB of record. While the IRB of record assumes responsibility for oversight and continuing review, the principal investigator (PI) and each institution are responsible for safeguarding the rights and welfare of human subjects as specified in 45 CFR 46 and/or 21 CFR 56. When an Oakland University investigator relies on an IRB at another institution, the Oakland University investigator should submit the following to the Oakland University IRB:

- A copy of the grant proposal, if applicable
- A copy of the entire IRB application submitted to and approved by the collaborating entity and all supportive materials as applicable (informed consent, HIPAA authorization, questionnaires, advertisements, and permission letters)
- Copies of IRB approval letter (s) issued by the collaborating entity

Section 1.2 Responsibilities of the IRB

(a) The Oakland University IRB is responsible for the protection of subjects participating in research. In reviewing research proposals, the IRB gives extensive consideration to each of the following components:

(1) Potential risks (physical, psychological, social, or economic) to research participants

(2) Anticipated benefits to the subjects and others

(3) The importance of the knowledge that may be reasonably expected to result from the research

(4) The consent process to be employed

(b) One of the major responsibilities of the IRB is to assess the risks and benefits of the proposed research. Risks to research participants should be justified by the anticipated benefits to the subjects or to society. This is a major guiding principle of the federal regulations. In addition to weighing risks and benefits of a proposed study, the IRB must determine that any risks to subjects are minimized to the extent possible. In order to make these determinations, the IRB must have complete information about the selection and recruitment of subjects and the procedures to be utilized. In addition, the IRB must assess whether the research design will yield useful data. Poorly designed research means that the risks are not likely to be reasonable in relation to potential benefits. Therefore the IRB needs full information about (1) the hypothesis to be explored, (2) the research design, and (3) the scientific rationale (including the results of previous human and animal studies, if appropriate). In addition, the IRB must determine that the investigators are competent to conduct research in the area being studied and that there are no potential conflicts of interest.

(c) Central to the ethical requirements underpinning research with human subjects is the principle of "Informed Consent." Informed consent assures that prospective human subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate. The IRB is also responsible for determining that subjects will be provided with an accurate and fair description of the study as well as all foreseeable risks or discomforts and any anticipated benefits. In addition, the IRB must determine that informed consent will be properly obtained from subjects and documented. For more information about obtaining informed consent, see Informed Consent {Part 3}.

(d) Other important responsibilities of the IRB are determining that the privacy of research participants is protected and that the confidentiality of the data is maintained through adequate safeguards. The IRB also determines intervals for periodic review of ongoing projects and, where considered appropriate, determines that adequate provisions are in place for monitoring informed consent and data collection. Researchers should be aware that research may be subject to intramural inspection or audit.

(e) Additional Safeguards for Special Populations {refer to Part 4} are required for research involving children, fetuses, pregnant or lactating women, human ova in-vitro fertilization, prisoners, persons with physical or cognitive impairments, or other potentially vulnerable groups (educationally-disadvantaged persons, terminally-ill patients, etc.). Federal regulations on research involving vulnerable populations strictly limit research presenting more than minimal risk or discomfort and require special IRB attention to procedures for obtaining informed consent. Minimal Risk is defined by the regulations as risk to subjects participating in the research does not exceed risks encountered in ordinary, everyday life or in the performance of routine medical, dental, or psychological examinations.

(f) Based on these considerations, the IRB has the authority and responsibility to approve, require modifications to secure approval, or disapprove all human subject research, before it is initiated, in order to comply with ethical principles and federal, state and local regulations and institutional policy. The IRB provides continuing oversight of all human subjects research, with all but exempt research protocols reviewed at least yearly. The IRB has the authority to assure on an ongoing basis, that the risks of proposed research are justified by the potential benefits to the participants and to society, that the risks do

not fall disproportionately on one group, and that risks are minimized to the extent possible consistent with sound research design. The IRB is authorized to oversee the consent process to ensure that agreement by an individual to participate in research is voluntary and knowing.

Part 2 Responsibilities of Researchers

(a) The individual researcher's primary responsibility is complying with federal regulations and ensuring the safety and welfare of subjects. Therefore, it is the responsibility of each investigator to become familiar with and understand the regulations regarding the use of human subjects in research. The Guidelines for Research Involving Human Subjects at Oakland University are designed to provide researchers with basic information about obtaining approval for research projects and the protection of human subjects. For complete information related to the federal regulations, researchers should refer to the Federal Guidelines for the Protection of Human Subjects in Research at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html (refer to 45 CFR 46, subpart a, b, c, and d).

(b) All PIs must complete mandatory training in order to conduct human subjects research at Oakland University. PIs and faculty sponsors must ensure proper training of their staff and students, respectively. The Collaborative Institutional Training Initiative (CITI) offers a variety of training modules for undergraduate and graduate students, faculty and staff, and IRB members. New applicants should log on to the CITI training site at https://www.citiprogram.org and complete the required training prior to submission of a new protocol application. It is recommended to retain a copy of the training completion report as it will be required for submission of a new protocol application through the online protocol submission system, IRBNet. PIs and faculty sponsors must also ensure the completion of other protocol specific training, as applicable. Supplemental training sessions are offered periodically throughout the academic year. Information about the training sessions can be obtained through the Office of Research Administration.

(c) If the investigator is not a regular faculty member, a regular faculty member must be designated as the responsible faculty member or special permission to serve as the PI must be obtained (see Section 2.2). In such a case, the responsible faculty member also incurs all responsibilities of the investigator.

Section 2.1 Obtaining Approval for Research Proposals

(a) Before conducting research involving human subjects, researchers must submit an application for the project to the IRB. The online system for submitting electronic applications is available on the Oakland University Research website or directly through the IRBNet website at http://www.irbnet.org. Training for use of this system is available on the Oakland University IRB website and in the step-by-step instruction guide located in the forms and templates library of IRBNet. All sections of the application and other required forms (including Conflict of Interest and Principal Investigator Assurance) must be completed prior to electronic submission. For projects that involve research conducted at other facilities with their own IRBs, such as hospitals or other universities, a copy of the approved submission materials, the IRB approval letter from that facility, and the IRB authorization agreement between the institutions must be forwarded to the Office of Research Administration. Research may not commence until approval has been received from all IRBs involved.

(b) Keep in mind that special consideration is required for all research involving children, fetuses, pregnant or lactating women, prisoners, persons with physical or cognitive impairments, or other potentially vulnerable groups (educationally-disadvantaged persons, terminally-ill patients, etc.). Investigators should review federal regulations specifically related to these groups (45 CFR 46 subparts b, c, and d) and review the section on Additional Safeguards for Special Populations {refer to Part 4} contained in this document.

(c) The involvement of human subjects in research, including recruitment, obtaining informed consent, and pilot testing, is not permitted until submission and approval of the projects by all IRBs involved. However,

researchers may contact organizations from which subjects will be recruited prior to receiving IRB approval.

Section 2.2 Submitting an Application for a Research Project to the IRB

(a) Research proposals may be submitted to the IRB by any regular faculty member of Oakland University (professor or associate professor). Non-tenure track faculty, students, staff, or individuals holding other titles (research associate, post-doctoral fellow, or visiting, clinical, or adjunct faculty) may submit proposals, but they must designate a responsible faculty member. Individuals from outside Oakland University occasionally may be allowed to conduct research within the university, but the proposal must be submitted and sponsored by an Oakland University faculty member and special permission must be obtained form the Vice Provost for Research. The "Request for Special Permission" form is available in the forms and template library of IRBNet and must be submitted with the application along with CITI training certification.

(b) The Oakland University IRB meets on a regular basis once a month. To be considered for review at a board meeting, a completed proposal and all required attachments must be uploaded into IRBNet seven to ten days before the next scheduled meeting date. IRB meetings are scheduled for the last Thursday of the month.

Section 2.3 IRBNet

Oakland University's Office of Research Administration has adopted the IRBNet suite of tools, accessible via the National Research Network, for management of on-line protocol submissions and many other important features integral to the oversight of human subjects research. All new protocols, amendments, continuing reviews, and other submissions pertaining to research studies must be submitted electronically via IRBNet. Communications and all review decision letters will also be issued electronically via IRBNet. IRBNet may be accessed from any computer using a web browser by visiting www.irbnet.org. Researchers must register in the system to establish a username and password. The IRBNet forms and templates library includes application forms, institutional guidelines for the conduct of human subjects research and instructions for using IRBNet. Researcher training for this system is available on the IRB website. The IRB Office may be contacted at (248)-370-2762 for additional information or training.

Section 2.4 Categories of IRB Reviews

(a) All research activities involving human subjects must be evaluated to determine the type of IRB review needed. Depending on the level of risk, there are three categories under which human subjects research may be reviewed. Studies which meet the criteria for "minimal risk" may qualify for exempt or expedited review. Minimal risk means that risk to subjects does not exceed risks encountered in ordinary everyday life or in the performance of routine medical, dental, or psychological examinations. If the project poses greater than minimal risk to research subjects, it must be reviewed by the fully convened IRB.

(b) If the project presents no more than minimal risk to the participants involved and, in addition, it does not compromise the privacy or confidentiality of the participants involved, it may be exempt from formal review. The project must be completely described by one or more of the following exempt review categories to qualify.

> (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
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> (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside

the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. Note that research with *children* involving surveys, interviews or behavioral observations in which the researcher participates does not qualify as exempt.

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

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

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

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

(c) If the research activity does not qualify for exempt status, but it presents no greater than minimal risks to subjects, it may qualify for expedited review. If all of the procedures will be carried out as described in the list of activities below, then the project may be reviewed through an expedited review procedure. However, if any of the activities described in the project are not to be found on the list, the project will need to go through a full committee review. Categories of <u>expedited</u> <u>review</u> for an initial submission include the following:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on 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.) (b) Research on medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine

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

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

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). This listing refers only to research that is not exempt.)

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

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

(d) In an expedited review, the application is generally reviewed by one or two committee members. If both reviewers concur that the activities present no more than minimal risk and meet the IRB criteria for approval, approval may be granted without full committee review. However, if a reviewer has concerns about potential risks to subjects or proposed procedures, the proposal will be referred for full committee review at the next scheduled IRB meeting.

(e) For research falling within the categories of exempt or expedited review, notification of approval will be forwarded to the PI within seven days of approval. If the project is referred for formal review by the full committee, the investigator may be contacted by the primary reviewer prior to the convened meeting to answer questions or provide clarification. In some cases, the investigator may be asked to attend the meeting if his or her presence would add substantively to the review. If the project is approved by a majority of IRB members attending the meeting, the PI will be sent notification in writing within seven to ten days of the meeting

Section 2.5 Modifying Approved Research

(a) Any proposed change in an approved protocol also must be reviewed and approved by the IRB prior to the implementation of these changes except where necessary to eliminate an apparent immediate hazard to human subjects. Proposed changes should be submitted to the IRB through IRBNet using the protocol amendment form available in the forms and templates library of IRBNet. The amendment should include

copies of the modified documents such as the protocol, the informed consent document and/or subject recruitment materials.

(b) Changes to approved research include, but are not limited to changes in study design, recruitment procedures, the informed consent document and information provided to subjects. Addition or deletion of key personnel, increases in study enrollment numbers, and changes in the approval period also require prospective IRB approval.

(c) The proposed changes to the research will be reviewed according to whether the changes are considered "minor" or "significant." Minor changes are changes that do not affect assessment of the risk and benefits of the study, substantially alter research aims or methodology, nature of subject participation, level of risk, proposed benefits, participant population, qualification of the research team, or the facilities available to support the safe conduct of the research. Minor changes can be reviewed through expedited procedures. Minor changes to an application approved originally by a full board may also be approved through an expedited review provided that the changes impose no more than a minimal increase in risk and add no additional procedures other than those that qualify for an expedited review. Changes which have the potential to affect assessment of the risks relative to the benefits of the study are considered significant and require full board review and approval.

Section 2.6 Renewing Approval and Study Completion

(a) IRB approval is valid for a maximum of one year; although the IRB can request approval more often depending on the level of risk posed by the study. Investigators wishing to continue to conduct the study and/or collect data on human subjects after the expiration date must apply for a "continuing review" from the IRB by completing a continuing review application form available in the forms and templates library of IRBNet. Two automatic electronic notifications of expiration of the project will be sent by IRBNet at 2 months and 1 month in advance of the anticipated expiration date. Projects needing continuing review will be reviewed in the same manner as the original proposal unless the category of review has changed. For continuing projects, approval will need to be renewed on a yearly basis

(b) Investigators must continue to submit continuing review reports on research projects in which all study interventions have been completed, but data analysis is not complete.

(c) The Oakland University IRB should be notified promptly of study completion by submitting a final report form available in the forms and template library of IRBNet.

Section 2.7 Minimizing Risks to Subjects

(a) Investigators must minimize risks to all subjects. A description of procedures to minimize risk, any alternate procedures to be used, and any procedures to aid subjects in the case of injury or other negative events must be included in the proposal. Researchers need to identify and attenuate as much as possible the following kinds of risks: physical, psychological, social, or economic harm.

(b) **Physical Harm** includes the potential for pain, discomfort, or injury from physical or medical procedures. Procedures used in most medical research usually result in no more than minor, transient discomfort (e.g., pain and minor bruising from venipuncture); however other research designed to evaluate new drugs or procedures may present more than minimal risk, and, on occasion, can cause serious or disabling injuries. Researchers must also be aware of the potential for negative consequences from changes in any underlying physical conditions from which the subject may suffer.

(c) **Psychological Harm** includes undesirable changes in cognition and emotion, such as feelings of stress, depression, guilt, embarrassment, or loss of self-esteem. These changes, usually transitory, can arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics or from filling out a questionnaire. Stress may be induced when researchers manipulate the subjects' environment (e.g., by

staging fake emergencies or fake assaults; by providing false feedback about subjects' performances, abilities, or personality; by deceiving subjects in other ways). The use of deception is justifiable only when using deception is the only way to answer the research question. In most instances when deception is used, subjects later need to be debriefed as to the nature of the deception, but this determination is made on a case-by-case basis.

Other psychological harm can result from invasion of privacy (access to a person's body or behavior without consent, as in observation of behavior that subjects consider private) and from breach of confidentiality (failure to safeguard information that has been given voluntarily from one person to another).

(d) **Social and Economic Harm** includes invasions of privacy and breaches of confidentiality, which may result in embarrassment within one's business or social group, loss of employment, or criminal prosecution. Areas of particular sensitivity include information related to alcohol or drug consumption, mental illness, illegal activities, and sexual behavior. Some information about individuals (e.g., actual or potential delinquency, mental illness status, HIV status) could label or stigmatize subjects' standing in the community and could adversely affect present or future employment or eligibility for insurance. At times, participation in research can result in extra monetary costs to subjects; these need to be described during the consent process.

Section 2.8 Maintaining Confidentiality

(a) It is the responsibility of the researcher to guarantee that information related to subjects is kept confidential. Investigators must follow all procedures outlined in their proposal for guaranteeing that confidentiality is maintained. This process includes procedures such as the use of coding, pseudonyms, or anonymous surveys and the storage of all information related to the project in a secure location available only to the investigators (or others as outlined in the consent document).

(b) For studies collecting protected health information (PHI), the Health Information Portability and Accountability Act (HIPAA) includes additional provisions for the maintaining patient confidentiality. No PHI may be used or disclosed for research unless a written authorization has been obtained from the research subject or the IRB has waived the requirement for an authorization.

(c) If the research involves the collection of sensitive information such as genetic information, drug use, or other illegal behavior, the investigator may obtain a Certificate of Confidentiality for the study from the National Institutes of Health. A Certificate of Confidentiality protects privacy by preventing the disclosure of private information even in the case of a valid subpoena from a court or administrative agency.

Section 2.9 Maintaining and Destroying Records

Investigators are responsible for maintaining adequate and accurate records of all activities relating to human subjects research. All records must be maintained for at least three years past the completion of the study or in accordance with sponsor, funding source, and/or regulatory requirements. For instance, HIPAA requires records to be retained for at least 6 years. It is the responsibility of the investigator to be cognizant of and comply with all applicable record retention requirements. After that time, records can be destroyed in such a manner as to continue to protect the identity of subjects (e.g., shredding documents that identify participants).

Section 2.10 Participating in Audits

Federal guidelines require that all IRBs establish procedures for overseeing the human subjects research process beyond the IRB approval process. One of those responsibilities is the establishment of audit procedures to ensure compliance with state and federal regulations, institutional guidelines, and ethical treatment of human subjects. Thus, investigators should be aware that their study may be audited to

document compliance with these requirements. These audits may be related to such issues as procedures for obtaining informed consent, maintaining confidentiality, adhering to data collection methods outlined in the study, and maintaining records for an adequate amount of time. Other issues may also be addressed based on the nature of particular studies.

Section 2.11 Unanticipated Problems

(a) Investigators are required to promptly report problems involving risks to human research subjects or others to the Oakland University IRB. Unanticipated problems are events or issues that are unforeseen, expose participants or others to increased risk of harm, and are related or possibly related to the research. Examples of unanticipated problems include, but are not limited to, serious adverse events, subject complaints, breaches of confidentiality, and noncompliance with federal regulations and institutional guidelines. Unanticipated problems must also be reported to the Institutional Official who is responsible for reporting to federal sponsors and agencies.

(b) Unanticipated problems include adverse events, but only those adverse events which involve harm or increased risk to a subject and which, in the opinion of the PI, are *unexpected* and possibly or probably *related to the research* should be reported. An adverse event is "unexpected" when its specificity and severity are not accurately reflected in the informed consent document or the protocol. An adverse event is "related to the research" if the principal investigator believes that it was more likely than not to be caused by the research procedures, or more likely than not that the event affects the rights and welfare of current research subjects.

(c) Some unanticipated problems and other events also constitute non-compliance, which is the failure to comply with applicable federal, state or local regulations or the requirements or determinations of the Oakland University IRB. Non-compliance can be intentional or unintentional, can result from action or omission, and may be minor or serious. A non-compliant activity can be a one-time event or, if repeated, may constitute continuing non-compliance. Examples of non-compliance include but are not limited to conducting research without prior IRB approval, misuse or nonuse of consent forms, failure to obtain informed consent, implementing changes to approved research without prospective IRB review and approval, and continuing to gather data after approval expires. Noncompliance may lead to suspension of the privilege of conducting research using human subjects and/or referral under University policies and procedures governing professional misconduct.

(d) Investigators are required to report any unanticipated problems to the IRB within 5 business days of becoming aware of the problem using the event reporting form in the forms and templates library of IRBNet. The report should include a description of the event, any harm or increased risk to subject as well as remedial actions taken and a risk mitigation plan to prevent the problem from occurring in the future.

(e) The Oakland University IRB has the responsibility to investigate the problem and ensure that future risks have been appropriately minimized. The Oakland University IRB will report the unanticipated problem to the appropriate Institutional Officials, who are required to report to federal sponsors and agencies.

Section 2.12 Special Responsibilities of the Faculty Mentors, the Responsible Faculty Member and Students

(a) Before submitting proposals for research planned by students, faculty have the responsibility of ensuring that students have received appropriate faculty input. Student researchers, like faculty, need to be able to explain all procedures employed in their study, risks and benefits of the project, and a rationale for their methods. For many students who may be just learning the research process, this could involve multiple proposal revisions and meetings with their advisor. Proposals for student research should not be submitted until faculty advisors are confident that their students understand and can justify their study based on input from their faculty advisor and any other faculty or staff that are involved in the study, and that all suggested changes have been incorporated into the proposal.

(b) Faculty investigators and responsible faculty members have the additional responsibility of ensuring that student researchers understand the federal guidelines for conducting research with human participants and complete the required CITI Training

(c) Student researchers also have the responsibility of ensuring that they understand the research they are proposing to undertake including all procedures employed in their study, risks and benefits of the project, and a rationale for their methods.

(d) Student researchers also have the responsibility of ensuring that they understand the federal guidelines for conducting research with human participants. Students must not conduct research until they are confident that they understand the federal rules and regulations pertaining to their research activities and complete mandatory CITI training before they submit their project to the IRB.

Section 2.13 Research Conducted as Part of Course Requirements for Advanced Courses, Teaching Research Methods and Assessment Techniques

At times, courses designed specifically to teach students how to conduct research or how to test and assess individuals may include research projects designed to give students training in research and assessment. If these projects include any "systematic, empirical investigations (including research development, testing, and evaluation) designed to develop or contribute to generalizable knowledge," and involve "human subjects" they need prior IRB approval. Projects intended to demonstrate research or assessment techniques and that are not designed to contribute to generalizable knowledge, need not be submitted to the IRB.

Section 2.14 Noncompliance

Noncompliance is failure to comply with applicable federal, state or local regulations or the requirements or determinations of the Oakland University IRB. Investigators must report any noncompliance to the Oakland University IRB per institutional guidelines as outlined in section 2.10.

Section 2.15 Conflict of Interest

(a) To maintain objectivity in research, all investigators and key personnel are required to disclose all financial conflicts of interest (FCOI) and conflicts of commitment to the IRB using the Conflict of Interest Disclosure Form available in the forms and templates library of IRBNet.

(b) An FCOI is a significant financial interest that may affect or appear to affect the design, conduct and reporting of research. Situations such as a financial interest in publically traded and non-publically traded companies as well as serving as a board member or executive with the sponsor of the research or a company with a financial interest in the results of the research represent just a few potential financial conflicts of interest.

(c) Significant financial conflict of interest will be determined by either the Oakland University or PHS policy and will apply to the investigator, the investigator's spouse and dependent children, and all key personnel.

(d) A conflict of commitment exists when research personnel's external activities or time or use of resources interfere with their responsibilities to their position at Oakland University.

(e) For PHS funded research, investigators must comply with all the requirements outlined in Oakland University's Office of Research Administration FCOI policy. When a FCOI is identified that is related to human subjects research and requires a management plan, the Vice Provost of Research or Designated Official will immediately forward the management plan to the Oakland University IRB. The IRB will consider the FCOI when reviewing the protocol, and may add (but not remove or decrease) requirements to

the management plan. The IRB must communicate any decision to increase the requirements of the management plan to the Vice Provost of Research or Designated Official, who will ensure that the investigator is notified about the revised management plan.

Section 2.16 Registration of Clinical Trials

(a) Investigators who initiate their own research studies and whose research meets the definition of a clinical trial must ensure the study is registered in a publically available database such as clinicaltrials.gov. The International Committee of Medical Journal Editors (ICMJE) defines a clinical trial as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome." This definition includes drugs, surgical procedures, devices, behavioral treatments and process-of-care changes. Member journals require registration of the clinical trial prior to enrollment of the first subject as a condition for publication. The responsibility for registering the trial lies with the investigator for investigator-initiated studies. Thus, it is important that investigators be aware of these requirements and ensure that studies that meet ICMJE's definition of a clinical trial are appropriately registered.

(b) The FDA Amendments Act (FDAAA) of 2007 has a similar requirement for registration of "applicable clinical trials." According to the FDAAA, applicable clinical trials include interventional studies of drugs, biologic products or devices that are subject to FDA regulations. The sponsor of the research is responsible for ensuring that the study is registered. This would include the PI in the case of investigator-initiated research.

(c) For clinical trials initiated on or after March 7, 2012, the FDAAA also requires that applicable clinical trials include the following statement word-for-word in the informed consent document: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time." The purpose of the informed consent requirement is to promote transparency in clinical research to research subjects and patients.

Part 3 Informed Consent

Perhaps the most important part of the IRB application is that containing the "Informed Consent" process. Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. The set of federal policy consent requirements are provided in 45 CFR 46 www.gpoaccess.gov/cfr/retrieve.html (request 45 CFR 46, section 116) and are described in the sections below. In addition, OHRP offers tips on consent forms at http://www.gpoaccess.gov/cfr/retrieve.html .

In view of the importance of informed consent, it is critical that the individual conducting the consent interview be knowledgeable about the study and trained in human subjects research. Furthermore, researchers should be reminded that informed consent is a process and not just a document. Informed consent begins with the investigator's first contact with the potential research subject and continues throughout the subject's participation in the research. Therefore it is critical to affirm the subject's willingness to continue participation throughout the study.

The consent process can be analyzed as containing three important elements: information, comprehension, and voluntariness.

Section 3.1 Elements of Informed Consent

(a) **Information** includes specific items for disclosure intended to assure that subjects will be given sufficient information. These items generally include: the research procedures, their purposes, risks and anticipated benefits, alternative procedures (where therapeutic intervention is involved), person(s)

conducting the research, and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.

(1) The extent and nature of the information {refer to 3.4} 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 scientific knowledge. Even when some direct benefit to subjects is anticipated, the subjects should understand clearly the range of risks and the voluntary nature of their participation.

(2) A special problem of consent arises when informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

(b) **Comprehension** includes the subjects' ability to understand what the research will actually entail. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration, or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

(1) Because the subject's ability to understand is a function of intelligence, rationality, maturity, and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be appropriate to give some oral or written tests of comprehension. To facilitate comprehension, ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms; hematoma as a bruise; venipuncture as drawing blood from your arm with a needle). When the subject sample is heterogeneous or includes racial or ethnic minorities, researchers need to be particularly sensitive to differences in language and cultural norms.

(2) Special provisions may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as not competent (e.g., infants and young children, mentally disabled patients, people who are terminally ill or comatose) needs to be considered individually. Even for these persons, however, respect requires giving them the opportunity to choose, to the extent that they are able, whether or not to participate in the research. The objections of these subjects to involvement should be honored unless the research entails providing beneficial therapy unavailable elsewhere. At times, respect for persons may require seeking the permission of other parties in order to protect the subjects from harm. Persons with severely limited comprehension are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

(3) The third parties chosen should be those who are most likely to understand the non-competent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research if such action appears in the subject's best interest.

(c) **Voluntariness** refers to the idea that consent is given voluntarily and is free of coercive elements. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Unjustifiable pressures may occur when persons in positions of authority or commanding influence urge a course of action for a subject. Coercion is likely to exist whenever possible sanctions are involved, such as an actual or implied threat to withdraw or decrease health-related or other services. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance. Moreover, incentives that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

(1) Many studies involve the use of incentives, usually monetary, for participation as a subject. All studies involving the use of participation incentives must include a description of procedures to ensure that participation is voluntary and must involve the use of reasonable incentives based on the subject population, the complexities of the procedures, and the amount of inconvenience to the subject.

(2) Additionally, investigators must avoid the use of language in their informed consent that implies coercion or undue influence. This includes language that makes the incentive sound so attractive that it creates undue influence by blinding prospective subjects to the risks, impairing their ability to exercise proper judgment, or prompting them to lie or conceal information that, if known, would disqualify them from enrolling or continuing as participants in the research project.

(3) Finally, the consent process may not involve the use of "exculpatory language" through which the subject or representative is (1) made to waive *or appear to waive* any of the subject's legal rights or (2) releases or *appears to release* the investigator, sponsor, institution, or agents from liability for negligence. Thus, statements, such as "there are no funds available for the treatment of injuries resulting from participation," which may be perceived as a waiver of legal rights by some subjects, are disallowed, unless they are followed by a clear statement that the subject is not waiving any legal rights to redress against the investigators, Oakland University, or other sponsors for injury resulting from negligence.

Section 3.2 Research Involving Students, Employees, and Normal Healthy Adults

(a) The federal regulations do not provide special protections for subjects in these categories, but investigators need to consider a number of factors related to obtaining informed consent from these individuals. First, volunteers for whom no therapeutic benefit can result from participation should be exposed only to risks that are minimized to the greatest extent possible. Second, the agreement to participate must be voluntary {refer to 3.1(c)}, and free of coercion or undue influence. Students, employees, and normal (i.e., healthy) volunteers should be recruited through general announcements or advertisements, rather than through individual solicitations, whenever possible, to minimize increased persuasiveness due to interpersonal contact or previous relationships with investigators.

(b) Researchers also need to consider carefully what will happen if and when subjects should become sick or injured during the research, particularly in the case of drug or other biomedical studies. Such issues should be clearly spelled out in the informed consent document and should be reviewed with each prospective subject. For example, subjects should be told whether any medical treatments will be made available should injury or illness occur and, if so, what they consist of and whether subjects are expected to pay for treatment of research-related injuries or illness.

(c) When subjects are students or employees, there are particular concerns about potential coercion, undue influence, and confidentiality. Students may feel they need to volunteer to earn a better grade, get a recommendation, and so forth. Alternatively, they may feel that unwillingness to participate would negatively affect their relationship with the investigator or faculty in general. Data collection on sensitive issues presents risks to subjects from which they should be protected to the greatest extent possible.

Similar issues arise for employees who may feel that they need to volunteer for reasons of performance evaluation or job advancement. It may also be difficult to maintain confidentiality of personal medical information or research data when the subjects are also employees. Investigators should ensure that these concerns are all appropriately addressed before enrolling students or employees on any research project.

Section 3.3 Basic and Additional Elements of the Consent Process

(a) Unless the IRB approves a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waives the requirement to obtain informed consent, federal regulations require that the following information or basic elements of consent are provided to each subject as part of the informed consent process:

1. 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.

2. A description of any reasonably foreseeable risks or discomforts to the subject.

3. A description of any benefits to the subject or to others, including scientific benefits, which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

5. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.

6. For research involving more than minimal risk, an explanation as to whether any compensation or medical treatments are available if injury occurs, and, if so, what they consist of, and whether subjects are expected to pay for treatment of research-related injuries or illness. As discussed above in the section on voluntariness {refer to 3.1(c)}, no exculpatory language may be used.

7. A statement of whom to contact for (a) answers to pertinent questions about the research (one or more of the investigators), (b) research-related illness or injury (the faculty investigator or the responsible faculty member), and (c) the rights of research subjects (IRB).

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) The regulations further provide that the following additional information or elements will be provided to subjects, where appropriate:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is pregnant or may become pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

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

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

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

6. The approximate number of subjects involved in the study.

7. For applicable clinical trials initiated on or after March 7, 2012, the FDA Amendments Act also requires that the informed consent document include the following statement word-for-word: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Section 3.4 Written Documentation of Informed Consent

(a) In most cases, federal regulations require that informed consent is documented in writing. Documentation usually involves the use of a written consent form containing all the basic and additional elements as described above. The consent form must be signed and dated by the subject (or the subject's legally authorized representative) and by the person obtaining consent. One copy of the signed and dated consent form should be given to the subject (or representative), and the other copy should be retained by the investigator for at least three years after conclusion of the study. Consent forms that include a HIPAA authorization must be retained for at least 6 years.

(b) Federal Regulations require that IRBs give special consideration to protecting human subjects who are particularly vulnerable. These subjects include children, prisoners, pregnant women, cognitively impaired individuals, prisoners, traumatized or comatose individuals, persons who are terminally ill and those who are economically or educationally disadvantaged. In addition, the use of fetuses or fetal material and research on human in vitro fertilization are also considered to fall into a special category. With the exception of research involving children, investigations using special populations are approved only when the research objectives cannot be met using populations outside this special category and when there is only minimal risk involved or when the research will directly benefit the subjects. Additional requirements for obtaining consent from special populations in research can be found below in the section entitled Additional Safeguards for Special Populations {Part 4}. The section on Special Research Domains {Part 6} includes provisions and safeguards for specific types of research.

(c) In some cases (e.g., if the subject is unable to read, or does not speak English), the information about consent may be presented verbally. In these cases, the researcher provides the subject with a written summary of what is presented orally and a short form written consent document. The written consent document should state that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When a short form is used, there should be a witness to the oral presentation. The short form must be signed by the witness and the subject or the subject's legally authorized representative. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness must sign both the short form and a copy of the summary, and the person actually obtaining consent must sign a copy of the summary. A copy of the summary must be given to the subject or the representative, in addition to a copy of the short form.

(d) In rare instances, the IRB may waive written documentation of the consent process (but not the process itself) for research presenting no more than minimal risk. For example, in cases in which the principal risk of the study consists of the potential for a breach of confidentiality concerning the subject's participation in the study (e.g., studies of extremely sensitive topics, such as sexual deviance or drug abuse or studies in which subjects reveal a positive HIV status), the IRB may waive written consent. In certain instances of research involving no more than minimal risk where the research could not be practically carried out if written documentation were required (such as telephone or web surveys), the IRB also may waive the

requirement for written documentation of informed consent. Waivers of written documentation of informed consent do not remove the need for obtaining informed consent following the guidelines for Information Required on Consent Forms {3.4}. When documentation of consent is waived or altered, the IRB must ensure that specific regulatory criteria are met.

(e) Specific cases may exist for which the requirement of obtaining informed consent from human subjects may be waived by the IRB. There may be times when the researcher proposes to use *archival data* or data that have been collected for other purposes, and anonymity and confidentiality is clearly maintained. Archival data may include observations, texts or analyses that pre-date the planned research project or were generated under the auspices of an institution or agency other than Oakland University. These data may include published results of an investigation (for meta-analysis), data gathered under action research projects that already have ethical clearance (re-analysis), or information both gathered and owned by other agencies. In some cases it may not be feasible, reasonable, or necessary for the researcher to obtain informed consent. The IRB will make this decision based on whether the research meets the following criteria:

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

(f) All research involving human subjects at Oakland University must be approved by the IRB, even in cases when informed consent may not be required.

Section 3.5 Administering the Consent Document

(a) The following are suggested guidelines for obtaining written documentation of informed consent: The consent process should be administered by someone knowledgeable about the study and trained in human subjects research. The consent process should be conducted in a private setting free from distractions. Attention should be given to whether special provisions are required for obtaining consent such as a surrogate decision maker or in the case of research with children, how assent will be obtained and whether the permission of one or both parents is required. The consent process should begin by providing the research subject with a copy of the informed consent document. The consent provider should explain the process of informed consent, the subject's role and responsibilities as a research subject as well as the voluntary nature of their participation. The subject should be informed that they are free to ask questions at any time during the consent process. The study purpose, risks, benefits, alternative and other elements of the consent process should then be discussed with the subject. Comprehension should be assessed throughout the consent interview by asking the subject questions. The subject should be given the opportunity to ask questions and be given time to consider whether or not they would like to participate. The subject should be encouraged to discuss their participation in the research with family and friends if needed. The consent form should be signed and dated in the presence of the consent provider. The consent provider should also sign and date the consent after the subject. The subject should be provided a copy of the signed and dated consent form. If the subject declines to accept a copy of the consent, the consent provider should provide contact information to the subject in case the subject has any questions or concerns about the study.

(b) The subject's research records should include additional documentation by the consent provider that no study related procedures were performed prior to the documentation of written informed consent.

Section 3.6 Constructing the Consent Document

The consent document should have three parts: beginning, middle, and end.

(a) *Beginning:*

(1) Who is doing the experiment?

(2) The nature, purpose, and duration of the research—including the fact that the procedure is experimental (if appropriate; e.g., clinical trials of new drugs and other experimental therapies).

(3) The uses to be made of the data.

(b) *Middle:*

(1) The methods to be employed.

(2) All foreseeable hazards, inconveniences, discomforts, and any potential risks to which subjects will be exposed.

(3) The availability of compensation and treatment, if injured.

(4) The benefits that might be expected.

(5) Disclosure of alternate procedures the subject may choose if the research involves therapeutic intervention.

(6) The conditions of participation (inclusion and exclusion criteria), if any.

(c) *End:*

(1) A statement that the data are confidential and a description of the procedures to be employed in maintaining confidentiality.

(2) A statement that (a) consent is voluntary and that a decision not to participate will not result in any prejudice or penalty and (b) that subjects are free to withdraw their consent or to discontinue participation in the research at any time without prejudice or penalty.

(3) An offer to answer any questions. Instructions for contacting an investigator (and the responsible faculty member if the investigator is a student) for research-related questions, the IRB for questions related to the subject's rights as a research subject, as well as someone to contact in the case of a research-related injury or illness (the faculty investigator or the responsible faculty member).

(4) Instructions for contacting an investigator (and the responsible faculty member if the investigator is a student) for research-related questions, the IRB for questions related to their rights as a research subject as well as someone to contact in the case of a research related injury or illness (the faculty investigator or the responsible faculty member).

(5) Date of signature fields for the subject and individual obtaining informed consent

Section 3.7 International Research

All human subjects research in which US investigators are involved must comply with the federal regulations for the protection of human subjects in all material respects. The IRB will approve international research as long as the procedures prescribed by the foreign institution afford protections to subjects that are at least equivalent to those provided in the federal guidelines. Additional guidance for international research in specific countries can be found at http://www.hhs.gov/ohrp/

Part 4 Additional Safeguards for Special Populations

Section 4.1 Children

(a) It is the policy of the National Institutes of Health that children should not be systematically excluded from studies on human subjects. It is in the best interest of child health and welfare that children be included where there is no specific reason for their exclusion. There are however, special guidelines for research involving children, and the categories of IRB reviews are somewhat different for adults and children. For example, research including surveys, interviews, and behavioral observations in which the researcher is a participant are not eligible for exempt review when the subjects are children. Additional information about review categories can be found in the section entitled Categories of IRB Reviews (Section 2.4). The procedures for obtaining informed consent are also somewhat different when children are involved as subjects.

(b) Federal guidelines require that parents of children under the age of consent (18 years in Michigan) give permission for their child to participate in research. In addition, federal guidelines also require that the child assent to participation. Assent is defined in the federal regulations as "a child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent." Even though minors are legally incapable of giving informed consent, they may possess the ability to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether or not they wish to participate in the research, particularly if the research (1) does not involve direct benefit to the subjects, and (2) the child can comprehend and appreciate what it means to be a volunteer for the benefit of others. If the research provides benefits to the child not available elsewhere, the IRB may determine that the child's assent is not necessary. The IRB will make a determination about the assent requirement on a case-by-case basis. A script of the assent language and content must be submitted to the IRB for approval.

(c) In some instances, the IRB may determine that the parents' interests do not adequately reflect the child's interests (e.g., research conducted on child abuse or neglect) and may waive the parental permission requirement. Some types of research require the permission of one parent; others require the permission of both parents. The following guidelines are provided to help researchers determine whether the permission of one or both parents is necessary:

Types of Research	Requirements
No Greater than Minimal Risk	Assent of Child and Permission of at Least One Parent
Greater than Minimal Risk with Prospect of Direct Benefit	Assent of Child and Permission of at Least One Parent
Greater than Minimal Risk and No Prospect of Direct Benefit	Assent of Child and Permission of Both Parents
All Other Research Needs Approval from the IRB and the Secretary of HHS who Consults Outside Experts	Assent of Child and Permission of Both Parents

For additional information, see http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd

Section 4.2 Pregnant Women (or Women Who Could Become Pregnant)

(a) Because of additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus, research involving women who are or who may become pregnant receives special

attention. In the case of research directed toward the mother (not the fetus), federal regulations require that no pregnant woman may be involved as a subject unless (1) the purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal. Women of child-bearing potential may be excluded from studies not only because of concern for the fetus, but also because of possible legal liability of sponsors and investigators for harm caused by investigational agents or other research activities. Consideration of the liability issue requires balancing the protection of women and potential fetuses against the benefits that would result from their inclusion (both direct benefits and benefits to others).

(b) Any study in which women of childbearing potential are possible subjects may inadvertently include pregnant women. Thus, when appropriate, subjects need to be provided with a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus) if the subject is or may become pregnant, which are currently unforeseeable, as part of the informed consent process. The IRB must determine whether the research would pose risk to a fetus (or nursing infant), and, in some cases, may need to ensure that subjects are advised to avoid pregnancy or nursing for a time during or following the research. In some instances, IRBs will require that subjects should be told to notify the investigator immediately if they should become pregnant; in others, potential risk may be sufficient to justify requiring that pregnant women be excluded from the study.

(c) In the case of research involving pregnant women, IRBs must determine when the informed consent of the father of the unborn child is also required. Special attention is justified because of the involvement of a third party (the fetus, who is a future member of society). The IRB must consider each research proposal involving pregnant (or potentially pregnant) women individually, weighing the risks and benefits to both mother and fetus before making a determination about consent. As a general rule, however, federal regulations require *both* the pregnant woman's and the father's consent unless one or more of the following applies:

(1) The purpose of the research is to meet the health needs of the mother. If the purpose of the study is to meet the health needs of a pregnant woman, her needs generally take precedence over the fetus, and her consent alone may be sufficient.

(2) The father's identity or whereabouts cannot reasonably be ascertained.

(3) The father is not reasonably available.

(4) The pregnancy resulted from rape.

Section 4.3 Fetuses

(a) Research involving the human fetus is subject to special federal regulations that guide IRB deliberations about fetal research (45 CFR 46 Subpart B). The fetus may also be an indirect subject of research, of course, when women who may be pregnant participate. Risks to the fetus from any research procedure generally must not be more than minimal (e.g., from ultrasound or changes in maternal diet). If the risks exceed the level considered minimal, they must be justified by anticipated benefit for the health of the mother or the particular fetus (i.e., therapeutic research), and the information must not be obtainable any other way. For additional information, investigators need to review the federal regulations at 45 CFR 46.204 (Research involving pregnant women or fetuses). All applicable federal, state, and local laws also must be followed (see Michigan statute addressing Data, Information and Research, MCLA 333.2685 et. seq.). For example, Michigan law states that nontherapeutic research may not be conducted on an embryo or fetus known by the person conducting the research to be the subject of a planned abortion being performed for any purpose other than to protect the life of the mother.

(b) For research involving the fetus ex utero, see 45 CFR 46 Subpart D (for viable fetuses, which are covered by the regulations for children) or 45 CFR 46.206 (for nonviable fetuses). For proposed research

involving the use of *any* material from a dead fetus, investigators also need to follow the guidelines found in 45 CFR 46.206. Information about fetal tissue transplantation research requirements can be found in the Federal Register 58:7457 (February 5, 1993).

Section 4.4 Cognitively Impaired Persons

(a) Cognitively impaired persons include individuals having a psychological disorder (e.g., psychosis, personality disorder), 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. Other persons, including those under the influence of alcohol or drugs (or alcohol or drug-dependent), 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 own best interests. In addition, these persons may be institutionalized, which may further compromise their ability to exercise voluntariness {3.1(c)}. Some institutionalized persons (particularly if institutionalized involuntarily) may decide to participate in research out of a desire to appear "rational" and "cooperative" to those making decisions about their release; thus subjects should be recruited from among non-institutionalized populations whenever possible. However, respect for persons argues that all adults, regardless of diagnosis, should be presumed competent to consent to participation in research unless there is evidence of serious mental disability that would impair reasoning or judgment.

(b) The general rule for research involving cognitively impaired persons is that research should involve these individuals only if: (1) they comprise the only appropriate subject population, (2) the research question focuses on an issue unique to subjects in this population, and (3) the research involves no more than minimal risk.

(c) Each case involving research on cognitively impaired persons requires careful IRB consideration, but, in general, IRBs do not approve research presenting more than minimal risk on these populations unless the research promises direct benefit to the subjects. If the research presents more than minimal risk, the IRB may consult the Secretary of Health and Human Services, who will request consultation from outside experts. If the research is likely to interfere with ongoing therapy or regimen, the patient's physician or other health care provider also will need to be consulted first.

(d) Persons who have been formally adjudged incompetent have a court-appointed guardian who must be consulted and who can give consent on behalf of the cognitively impaired person. A conflict-of-interest is perceived to exist, however, if this individual is an official of an institution in which the subject resides. When a legally appointed guardian is unavailable or a potential conflict of interest exists, researchers generally consult with close family members, such as a spouse or an adult child to obtain consent. If family members are to be used to obtain consent, however, it must be absolutely clear that the family members are acting in the best interest of the subject. Sometimes, family members or others financially responsible for the patient may be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances. Also, researchers need to be aware that the extent to which family members may legally consent to the involvement of impaired individuals (especially in cases where the research is not expected to be of direct benefit to subjects) is unclear.

(e) When it is deemed reasonable by the IRB, the subject's assent also may be solicited. Procedures can sometimes be developed to enhance the possibility that subjects can consent for themselves. IRBs often require competence (or incompetence) to be assessed, rather than assumed. The setting in which consent is sought and the person seeking it can influence a potential subject's ability to comprehend or appreciate what is being asked. A noisy, public, or uncomfortable setting or a disliked medical person can create anxiety or resistance that would not exist if the information were presented by another individual, at another time, or in another place. At times, the IRB may wish to appoint a "consent auditor" to monitor the consent process and determine whether proposed subject's consent, assent, or objection to participation in research. Finally, it is particularly important to protect the privacy and the confidentiality of information exploring emotionally sensitive topics in these institutionalized individuals. Many patients do not want even the fact of their institutionalization divulged.

Section 4.5 Prisoners

(a) Prisoners include all individuals involuntarily confined in a penal institution, including persons (a) sentenced under a criminal or civil statute, (b) detained pending arraignment, trial, or sentencing, and (c) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution. Research involving prisoners as subjects is limited to the following:

(1) Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior.

(2) Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or prisoners as incarcerated individuals.

(b) With documented approval from the Secretary of Health and Human Services, who will request consultation from outside experts, it *may* be possible to conduct the following types of research:

(1) Research on particular conditions affecting prisoners as a class.

(2) Research involving a therapy likely to benefit the prisoner subject.

(c) Much of the permissible research is behavioral. Biomedical research concerning, for example, the effects of limited exercise or prison diets on the overall physical condition of inmates may also be permitted, provided that the research procedures present no more than minimal risk. Minimal risk is defined somewhat differently, however, in the case of incarcerated individuals. The risks to which prisoners may be exposed by participating in research is not compared with the risks normally encountered by *prisoners*, but rather with risks normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy *persons*, i.e. non-prisoners.

(d) Research using prisoners as subjects is strictly limited because incarceration may directly conflict with the principle of autonomy. Several issues are of major importance in determining whether prisoners can freely consent to participate in research. Prison circumstances often create an environment that favors participation. For example, bad living conditions, poor or nonexistent medical care, and the lack of control allowed prisoners can create an undue influence on prisoners to volunteer for research. Participation in research under these circumstances may influence prisoners by moving them to special units where the living conditions are better than those of the general population. Alternatively,, when prisoners must earn money to purchase personal hygiene and other items, the chance to earn money through participating in research may constitute an undue inducement. Even the opportunity to leave the prison cell and interact with people from the outside may act as an undue influence on the decision to participate in research. Such inducements may blind prisoners to the risks of participation.

(e) In addition, confidentiality is extremely difficult or impossible to guarantee in prison environments. For example, it becomes public knowledge whenever inmates are moved around. Furthermore, prison records, including medical records, are accessible to persons who in other settings would not have access to such personal information. For these reasons, the research design, the rationale, and the informed consent process are carefully scrutinized by IRBs and by OHRP.

For additional requirements see: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc

Section 4.6 Traumatized and Comatose Patients

(a) Research on comatose patients or patients undergoing emergency care differs from clinical research in other settings because the patient's capacity to give informed consents is often severely compromised, and decisions about participation may have to be made too quickly to obtain permission from the patient's legally authorized representative. Altered mental status may vary from one of confusion and disorientation to coma. Altered mental status can result from an accident or emergency condition, a physiological response such as shock or infection, a psychological response (anxiety, grief, or physical pain), or the effects of drugs. In addition, a variety of state laws concerning informed consent for emergency treatment may be applied to research on therapies for emergency patients.

(b) Federal regulations permit a waiver of informed consent only in the case of research that presents no more than minimal risk. The FDA, on the other hand, does permit exceptions from the informed consent process for patients confronted by a life-threatening situation where there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the subject's life. Further information about FDA guidelines may be found in the section on Food and Drug Administration Regulations and Policies {5.1}. However, Federal regulations do not limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local laws.

Section 4.7 Terminally Ill Patients

(a) Terminally ill patients are those who are considered to be deteriorating from a life-threatening disease or condition for which no effective standard treatment exists. If an alternative subject population exists, it is generally considered unacceptable to conduct research using terminally ill individuals. At times, however, it may be necessary to use terminally ill patients in order to conduct research concerning their disease and its treatment. On certain occasions, it can be extremely beneficial to allow terminally ill patients to participate in clinical trials or allow them access to drugs currently being tested in other investigations through the FDA's "parallel track" mechanism. Research participation or expanded access to research drugs is sometimes the only means for terminally ill patients to benefit from investigational new devices or new drug treatments that may prolong life.

(b) Terminally ill patients must be protected at all times from coercion and undue influence, but they should not be automatically excluded from research in which they may want to participate. There may be instances when altruism and a desire to bring good from adversity may motivate terminally ill patients to become involved in biomedical or behavioral research. Some terminally ill patients may find participation in research a satisfying way of imparting some good to others out of their own misfortune. At the same time, it should be recognized that terminally ill patients are especially vulnerable because of a real or perceived belief that participation is necessary to receive continuing care from health professionals or because they might feel that any treatment is better than none. To minimize the possibility of coercive influences, IRBs frequently require the clinical investigator to be someone other than the patient's own physician.

(c) IRBs pay particular attention to the consent process--the setting and the manner in which risks and benefits are discussed. Potential subjects need to be advised accurately about all factors that might influence their decision, such as potential risks (e.g., drug toxicity), financial costs that might accrue to the patient, whether or not participation in the study is a condition for treatment in the institution, and whether or not monetary compensation compromises voluntariness. Accurate information concerning risks and benefits needs to be conveyed clearly and in a manner that will neither engender false hope nor eliminate all hope.

Part 5 Investigational New Drugs and Investigational Devices

Section 5.1 Food and Drug Administration Regulations and Policies

(a) Research investigating products regulated by the Food and Drug Administration (FDA), including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products, often require approval from the FDA as well as the IRB. The requirements for IRBs in the FDA regulations http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50 are identical to requirements in the regulations of the Department of Health and Human Services (DHHS). Whenever a protocol is subject to review under both FDA and DHHS regulations, both sets of regulations apply, and the requirements of both sets of regulations must be met.

(b) FDA requirements for obtaining informed consent from subjects are the same as those within DHHS, with the following exceptions:

(1) FDA (but not DHHS) provides explicit guidance for an exception from the informed consent requirements in emergency situations.

(2) FDA makes no provision for waiving or altering elements of informed consent because the types of studies that would qualify for waiver are either not regulated by FDA or are covered by the emergency treatment provisions.

(3) FDA (but not DHHS) explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records as they pertain to the study.

(c) In special situations, FDA regulations allow the agency to agree to waive the requirement for IRB review (but not the requirements for informed consent) if it is determined to be in the best interests of subjects, and alternative mechanisms for assuring the protection of the subjects are adequate. Investigators can apply for a waiver from FDA. If a waiver is granted, investigators need to notify the Chair of the IRB in writing and attach a copy of the waiver. Oakland may still require IRB approval on a local level even if a waiver from FDA is granted.

(d) It is the responsibility of researchers to be aware of all FDA (as well as DHHS) regulations that may apply to their proposed research. Clinical trials of experimental (i.e., unapproved) new drugs and other biologics, including biological products used *in vitro* for diagnostic purposes, as well as experimental medical devices are regulated by the FDA, and investigators must gain permission to test their effectiveness on humans by submitting either an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE). Investigations using approved, marketed drugs, biologics, and devices may require submission of an IND or IDE for FDA approval. However, according to federal regulations cited under 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND *if all six of the following conditions are met*:

(1) It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.

(2) It is not intended to support a significant change in the advertising for the product.

(3) It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

(4) It is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively).

(5) It is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7).

(6) It does not intend to invoke an exception from informed consent requirements for emergency research (21 CFR 50.24).

(e) In addition, clinical trials involving drugs intended solely for tests *in vitro* or in laboratory research animals are exempt from the requirements for INDs as long as they are shipped in accordance with 21 CFR 312.160. *In vitro* biologic products, such as blood grouping serum, reagent red blood cells, and anti-human globulin are also exempt from these requirements if they are intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and are shipped in accordance with 21 CFR 312.160. Special provisions for bioavailability or bioequivalence studies in humans may be found in 21 CFR 320.31.

Section 5.2 Additional Guidance for Drug Trials

(a) Once a drug is identified as having a potential effect on a disease state, it is tested first in animals. If animal testing indicates that the drug can safely be tested in humans and that the chemical may be therapeutically useful, the drug sponsor will submit an IND to the FDA–to begin testing in humans. The drug development process generally includes 4 phases. For further information, see 21 CFR 312 and 21 CFR 314. Clinical trials (also called "randomized clinical trials") are controlled; one group receives the drug while a control group receives either another treatment or no treatment (placebo). Participants are randomly assigned to either the experimental or the control group. The trials are either "single-masked" or "double-masked" (also called "single-blind" or "double-blind"), so that the investigator, the subject, or both, do not know who is in the treatment or control group until the study is concluded.

(b) In general, the control treatment must be the best standard therapy currently available for the condition being treated; however, placebos may be used in cases where there is no known or available (i.e., FDA-approved) alternative therapy than can be tolerated by subjects. In cases where the disease is lethal or seriously debilitating, use of placebos is rarely justified. Once there is good evidence to support the efficacy of a trial therapy, continued assignment to the placebo condition is considered unethical.

(c) A primary ethical concern is one of fairness. Researchers should understand and abide by the following guidelines:

(1) If the trial therapy is known to be superior to currently available therapies (as indicated by prior research), it is unethical to assign subjects to the inferior treatment.

(2) It would be unethical to perform a clinical trial comparing two treatments when there is a third therapy that is known to be superior to either or both (unless there is some reason why that therapy is not useful for the study population).

(3) However, clinical trials comparing two or more efficacious drugs may be justified if there is a dispute among experts about which drug is superior in all relevant aspects.

(d) In reviewing proposals, the IRB must first consider whether (1) the protocol is scientifically sound and (2) whether sufficient information has been obtained from the literature (relevant human and animal studies) and from the FDA to define, as far as possible, the potential risks to human subjects and the precise need for studies involving human subjects. In addition, the IRB must consider whether (3) the investigator has the appropriate qualifications, experience, and facilities to ensure that all aspects of the trial and follow-up will be conducted rigorously and with due regard for the safely and well-being of the subjects. The IRB must determine whether there are sufficient safeguards for (1) ensuring confidentiality of data, (2) providing ongoing surveillance of the drug's effectiveness and safety, and (3) notifying subjects and

physicians of significant risks. The IRB also needs to determine that (4) appropriate FDA review and clearance has been obtained, and (5) appropriate measures have been adopted to ensure that subjects understand the objectives and consequences of participation, particularly any risks that may be involved and alternatives that may be available.

(e) Attention to the informed consent process is of particular importance in randomized clinical trials. In addition to assuring that initial consent is properly obtained, the IRB must also determine whether continuing consent is necessary at critical intervals during the study (e.g., when the protocol is changed or new information about risks or benefits becomes available). When assignment to groups is random, subjects must be informed about the nature of the study design, and the method of treatment assignment (including the probability of assignment to the various groups). Subjects need to be fully informed about what treatments are possible and the implications of being assigned to each one of the groups (including the possible consequence of receiving the less effective intervention). When the appropriate conditions are met, investigators should consider using a "placebo washout" design, a "cross-over" design, or a "historical control" design.

(f) If the alternative treatment in a randomized clinical trial is a placebo, subjects must be informed. The placebo condition must be described in understandable terms as well as the probability of being assigned to the placebo group. Subjects also need to be informed about who will know their treatment assignment. In a double-masked study, for example, subjects should be told that neither they nor the investigator will know whether they are receiving the placebo or the experimental therapy, but the code may be broken, if necessary, by an outside person. The informed consent of vulnerable subjects (e.g., desperately-ill persons) must be particularly safeguarded; however, these same individuals should not be precluded from the chance for receiving potentially beneficial treatment solely on the basis of their vulnerability. In research involving clinical trials, IRBs have special concerns about confidentiality and privacy issues, particularly if a scientist will need to review many patient records containing sensitive medical information before selecting potential study subjects. Some investigators advertise for potential subjects, and the IRB must approve the wording of these advertisements to ensure that the investigator or sponsor does not make claims regarding the safety or efficacy of investigational drugs and devices for which they are being investigated [see 21 CFR 312.7(a) and 21 CFR 812.7(d)]. Payment to subjects for their participation in drug trials is common, and the IRB must carefully scrutinize both the method and the amount of payment to ensure that it fairly reflects the degree of risk, inconvenience, or discomfort associated with participation, but is not an undue influence.

Section 5.3 Medical Devices

(a) Medical devices are defined as diagnostic or therapeutic articles that do not achieve their principal intended purposes through chemical action in or on the body. Such devices include diagnostic test kits, pacemakers, intraocular lenses, and orthopedic equipment, and, as noted above, they are regulated by the FDA and must be cleared by that agency before the device can be marketed. Ranging from most to least safe and effective, medical devices are classified as Class I, Class II, or Class III, depending on several criteria: See 21 U. S. Code §360(c), Food, Drug, and Cosmetic Act §513 for additional information. Clinical trials of investigational medical devices require an approved IDE (21 CFR 812).

(b) In reviewing studies involving medical devices, the IRB must make two determinations: (1) whether a device study presents significant or nonsignificant risk; and (2) whether the study should be approved. Studies in which the device is determined to present nonsignificant risk may begin without submission of an IDE application to the FDA, and require approval only from the IRB; although the FDA may overrule an IRB decision of nonsignificant risk, requiring the sponsor to apply for an IDE. Significant risk device studies require both FDA and IRB approval.

(c) In general, a significant risk device is one that falls into one or more of the following categories:

> (1) The device is intended for use as an implant and presents a potential for serious risk to the health, safety, or welfare of the subject (including any risks associated with surgical implantation).

(2) The device is represented to be of use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of the subject.

(3) The device is intended for a use that is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of the subject.

(4) The device otherwise presents a potential for serious risk to the health, safety, or welfare of the subject.

Part 6 Special Research Domains

Section 6.1 Radioactive Materials and X-rays

(a) IRBs distinguish between radiation exposure resulting from routine medical management of a patient and radiation exposure that is part of research investigations. Exposure stemming from medical treatment is generally considered to have more benefits in relation to risk. Research involving radioactive material, including radiopharmaceuticals and machinery producing ionizing radiation must be approved by the Oakland University Radiation Safety Committee http://www.oakland.edu/research (go to regulatory compliance [radiation safety]). Because the actual effects of radiation exposure at low levels cannot be determined, the IRB ensures that risks of radiation exposure are minimized, according to the principle known as ALARA, "as low as reasonably achievable" (but see also 21 CFR 361.1 [b][3] for limits on radiation doses for adults and children). Researchers contemplating the use of radioactive materials or x-rays may need to be familiar with Nuclear Regulatory Commission requirements found in 10 CFR 19, 10 CFR 20, and 10 CFR 35.

(b) Radioactive drugs, kits, or generators that are to be used for investigational diagnostic or therapeutic purposes, including testing to establish their safety and effectiveness, will need an approved IND from the FDA. Exceptions are made for radioactive drugs used in certain research designed to study the metabolism of the drug or to gather information about human physiology, pathophysiology, or biochemistry--but not intended for immediate therapeutic, diagnostic, or similar purposes (21 CFR 361.1). See also 21 CFR 312.2(b) for certain exemptions from IND application requirements. In making a determination, IRBs take into account factors such as the maximum allowable exposure for occupational workers suggested by the National Council for Radiation Protection and Measurement and the Nuclear Regulatory Commission and exposures from familiar medical procedures, such as chest x-rays. Particular safeguards are necessary to protect human fetuses, particularly embryos, from exposure to radiation; therefore investigators will need to include procedures that preclude, to every extent possible, the use of pregnant women as subjects. Potential for genetic damage suggests that sex organs be protected from radiation.

(c) Additional risks are also associated with intravascular administration of contrast agents used in x-ray procedures; these risks vary with the contrast agent used and the age and disease state of the subject. The chemical structure of these agents, while not radioactive, can produce a number of adverse reactions, some of which may be severe or even life-threatening in certain individuals. Thus, investigators need to have adequate procedures for screening subjects and excluding those who may be at increased risk.

(d) In addition, IRBs are strongly concerned about informed consent. They must determine that subjects are given sufficient information to decide whether or not to participate even though the actual risks may be unknown. It is generally considered helpful to provide subjects with comparisons of experimental radiation dosage to that of familiar activities, such as air travel.

Section 6.2 AIDS and HIV-Related Research

(a) Because of its high rate of mortality, biomedical and behavioral research centering on the prevention and cure of AIDS and its precursor, HIV, has become a national priority. Still, such research presents many ethical concerns. One of the major concerns relates to confidentiality, since breaches in confidentiality could have severe adverse consequences, such as loss of employment or insurance coverage,

or criminal charges. Therefore, OHRP requires that patient identifiers be used only when absolutely necessary for the design of the study. When recorded, they should be stored separately from the data and used only when necessary. Lists of persons who elected not to participate should not be retained. In general, information is not to be disclosed without the subject's consent. Subjects need to be told who is entitled to see the records with identifiers, both within and outside of the project. This statement must take into account the possibility of review of records by funding or other regulatory agencies, such as DHHS or FDA. Researchers may need to seek legal advice about protecting subjects from disclosure of information to government agencies or disclosure to law enforcement, should they decide to subpoena information. Sometimes, a "certificate of confidentiality" can be sought from a federal or state agency to protect subjects. For more information regarding certificates of confidentiality, see http://grants.nih.gov/grants/policy/coc/.

(b) Clinical trials of HIV-related drugs, vaccines, or other therapies need to follow carefully the guidelines in the sections for Food and Drug Administration Regulations and Policies {5.1} and Drug Trials {5.2}. When subjects (and/or their partners) will be informed about subjects' HIV serostatus, appropriate pretest and posttest counseling must be provided by qualified counselors. HIV/AIDS-related research using infected individuals presents many, serious concerns about acquiring informed consent, particularly if the research involves promising treatments. For example, the fatal nature of the disease leaves AIDS patients in a desperate position in which many will seek any promising treatment. In addition, special concerns arise because of special vulnerabilities of groups that are overrepresented in rates of infection: homosexual and bisexual men, intravenous drug users, minorities, and, increasingly, women and children. Complicating the issue is the fact that HIV-related illness can cause dementia in later stages, necessitating additional safeguards for cognitively impaired persons [4.4]. Researchers working with HIV-infected persons must be capable of dealing with social, cultural, emotional, and psychological, as well as physical factors and should seek the advice and consultation of experts in these fields.

Section 6.3 Human Genetic Research

(a) Human genetic research involves the study of inherited human traits. Much of this research is aimed at identifying DNA mutations involved in causing specific health problems. There are four general categories of genetic research, forming a continuum:

(1) Pedigree studies to discover the pattern of inheritance of a disease and to catalog the range of symptoms involved

(2) Positional cloning studies to localize and identify specific genes

(3) DNA diagnostic studies to develop techniques for determining the presence of specific DNA mutations

(4) Gene therapy research to develop treatments for genetic disease at the DNA level

(b) The ethical issues raised by genetic research in the first three categories primarily concern the management of psychologically and socially potent personal genetic information. Genetic research often involves related individuals, and information affecting one subject can have direct implications for other family members. Other ethical issues as well as physical risks emerge when the results of these studies are used to develop and test gene therapies. The following should be considered.

(1) In categories 1-3 (above), researchers need to consider the potential for psychological, social, and economic risks to subjects. Learning that one is affected by a genetic disorder that has not yet manifested itself can be highly stressful, and investigators will need to provide for adequate counseling by persons skilled in communicating the meaning of genetic information. There is currently a debate among experts about disclosure of genetic information to subjects. Many believe that subjects should be allowed to decide whether or not they will receive this kind of information; others believe that subjects (and even relatives) should be told about the probability of future genetic conditions, especially if they are potentially dangerous or life threatening. Social

risks of learning this kind of information, including stigmatization, discrimination, and labeling, also may be ameliorated by genetic counseling. Subjects need to be told both the known and potential risks of participation, and researchers must discuss with subjects the assurances that can be given to protect confidentiality and instances in which assurance cannot be given (e.g., subpoena of information).

(2) The Genetic Information Nondiscrimination Act (GINA) is a Federal law that was passed in 2008 to prevent discrimination in health coverage and employment based on genetic information and this law applies to research. GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance. In addition, GINA's provisions prohibiting discrimination by employers based on genetic information generally do not apply to employers with fewer than 15 employees. Research subjects participating in genetics research should be informed of the protections and limitations afforded by GINA during the consent process.

Section 6.4 Research Involving Alcohol or Drug Use

(a) Research on alcohol or the use of other potentially-addictive substances (i.e. illegal drugs) can raise special IRB concerns, particularly when the research involves the administration of these substances and/or recruits persons who are drug or alcohol abusers. It is important for researchers to assess whether participation of the proposed population is likely to expose the subject to harm and the degree of potential harm. Clearly, risks may vary for abusers and non-abusers. Other problems occur when drug dependent persons or alcoholics who are active drinkers are recruited. For example, competence of alcoholics who are actively drinking to provide informed consent is questionable and must be directly assessed during the consent process to determine whether or not subjects need to be considered as cognitively impaired persons [4.4]. Researchers may have a number of special responsibilities with these populations (e.g., medical backup personnel may be required; provisions may be needed to eliminate the risk of drug or alcohol impairment before the subject leaves the research site, and so forth.

(b) The National Advisory Council on Alcohol Abuse and Alcoholism has issued guidelines called *Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation* (1989). Many of the recommendations apply equally well to studies involving the administration of other substances having the potential for abuse. In some research, for example, the Council advises that investigators have a special obligation to facilitate the entry of alcoholics who are active drinkers into treatment programs.

(c) Researchers also must exercise special care to avoid taking advantage of drug-dependent or alcohol-dependent persons, who may be easily available and economically and socially disadvantaged. Remuneration for participation, if offered, must be commensurate with the burden of participation only. Many potential participants may be unemployed, necessitating special concerns that even small remuneration may unfairly induce their participation. If the subject population includes adolescents, additional regulatory protections for Children [4.1] must be employed.

(d) Special precautions are needed to protect the confidentiality of data indicating alcohol abuse or use of illicit drugs. Subjects must be clearly informed about the nature of procedures to protect their privacy (including the fact of participation in drug or alcohol treatment programs). Sensitive information that can be linked to individual subjects should be safeguarded, and the release of such information to others for any purpose should be allowed only when continued confidentiality is guaranteed. A certificate of confidentiality may be requested from appropriate government officials to protect sensitive information from forced disclosure. The consent document must spell out clearly what kind of information can and cannot be released and to whom.

Section 6.5 Research Involving Coded Private Information or Biological Specimens

(a) Under the definition of human subject at 45 CFR 46.102(f), obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

(1) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and

(2) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

(b) In general, OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, OHRP does not consider research involving **only** coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

(1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

(2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:(a) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);(b) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

(3) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

(c) This guidance applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

(d) In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects under the HHS regulations. Unless this human subjects research is determined by the IRB to be exempt under HHS regulations at 45 CFR 46.101(b), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent under HHS regulations at 45 CFR part 46.116(c) or (d).

(e) OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether research involving coded private information or specimens constitutes human subjects research. The person(s) authorized to make the determination should be knowledgeable about the human subject protection regulations. In addition, the institution should ensure the appropriate communication of such a policy to all investigators. OHRP recommends that investigators not be given the authority to make an independent determination that research involving coded private information or specimens do not involve human subjects.