

Ohio University

Institutional Review Board Guidelines

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DEFINITIONS

Adverse event is an undesirable and unintended, though not necessarily unanticipated injury or physical or emotional consequence, to a human subject.

Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent [45 CFR 46.402(b)].

Certification means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance. [45 CFR 46.102(a)]

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. [45 CFR 46.402(a)] In Ohio the age of majority is 18 years.

Clinical investigation in the context of FDA regulations (not all clinical research is subject to FDA jurisdiction) means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]

Clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. [45 CFR 46.102(b)]

Covered Entity: This is the term that the HIPAA regulations use to describe the businesses in the health care industry that are subject to HIPAA regulations. Specifically, covered entities are health plans, health care clearinghouses and health care providers who transmit any health information in electronic form in connection with the following transactions: health care claims or encounter information, health care payment and remittance advice, coordination of benefits, health care claim status, enrollment or disenrollment or eligibility information re health plans, health plan premium payments, referral certification and authorization, first report of injury, or health claims attachments.

Emergency use means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(D)].

Family member means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship [21 CFR 50.3(m)].

Fetus means the product of conception from implantation to delivery [45 CFR 46.202(c)].

Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity,

spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord [45 CFR 46.202(a)].

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care [45 CFR 46.402(e)].

Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens [45 CFR 46.102(e)(1)].

The FDA also clarifies that the definition of a human subject includes those living individuals who are “controls” in a study and includes healthy individuals in a study (i.e., is not limited to “patients” or to those receiving an intervention) [21 CFR 50.3(g), 21 CFR 56.102(e)].

Institution means any public or private entity, or department or agency (including Federal, State, and other agencies). [45 CFR 46.102(f)] 21 CFR 50.3(h) and 21 CFR 56.102(f) are the same as above with the additional sentence: “The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.”

Institutional Review Board (IRB) means an Ohio University committee formally designated by the University to review, to approve the initiation of, and to conduct periodic review of, research involving human subjects. The primary purpose of such review is to protect the rights and welfare of the human subjects.

IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements. [45 CFR 46.102(h)] 21 CFR 56.102(m) is the same except that the term “clinical investigation” is used in lieu of “research.”

Intervention includes both physical procedures by which information or biospecimens 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 [45 CFR 46.102(e)(2), 45 CFR 46.102(e)(3)].

Investigator means an individual who actually conducts research or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

In vitro fertilization means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research [45 CFR 46.102(i)].

Minimal risk (for human subjects other than prisoners) means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [21 CFR 50.3(k), 21 CFR 56.102(i), 45 CFR 46.102(j)].

Minimal risk (for human subjects who are prisoners) is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons [45 CFR 46.303(d)].

Neonate means a newborn [45 CFR 46.202(d)].

Viable as it pertains to the neonate means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in the research only to the extent permitted and in accordance with the requirements of subparts A and D of this part [45 CFR 46.202(h)].

Nonviable neonate means a neonate after delivery that, although living, is not viable [45 CFR 46.202(e)].

Parent means a child's biological or adoptive parent [45 CFR 46.402(d)].

Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].

Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery. [45 CFR 46.202(f)].

Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [45 CFR 46.303(c)].

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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record) [45 CFR 46.102(e)(4)].

Protected Health Information (“PHI”): HIPAA defines protected health information (“PHI”) as individually identifiable health condition, health care and health care payment information, including the demographic data that is a potential identifier of the individual, maintained in the records of “covered entities” for treatment, payment and healthcare operations purposes. (See definition of “covered entity” above. Most health care providers and health plans and health care clearinghouses are covered entities) PHI does not include individually identifiable health information in personnel records or education records covered by the Family Educational Right and Privacy Act (“FERPA”).

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities [45 CFR 46.102(l)].

Serious Adverse Event (SAE) is one which is fatal or life threatening; results in significant or persistent disability; requires or prolongs hospitalization; results in a congenital anomaly/birth defect; or, represents

other significant hazards or potentially serious harm to research subjects or others [See also “Adverse Event”].

Sponsor is an entity external to the university that is providing support for a university research project pursuant to terms and conditions in an agreement between the sponsor and the university. With respect to FDA regulations, “sponsor” means the person or entity that has responsibility for fulfillment of FDA requirements for a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators [21 CFR 50.3(e) and 21 CFR 56.102(j)].

Sponsor-investigator (with respect to FDA regulations) means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, for example, corporation or agency. [21 CFR 50.3(f)] 21 CFR 56.102(k) is the same as above with the additional sentence: “The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.”

Test article means any drug (including a 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 and 354-360F of the Public Health Service Act [21 CFR 50.3(j) and 21 CFR 56.102(l)].

Unexpected or unanticipated refers to adverse events or other problems in the research, the specificity or severity of which is not consistent with the information already provided to the IRB, including the investigator’s brochure, research protocol or consent form.

Unanticipated Problems (UP) may or may not include specific events experienced by individual subjects, but are developments within the research activity that suggest a potential for increased risks to subjects or others.

Written, or in writing, for purposes of this part, refers to writing on a tangible medium (e.g., paper) or in an electronic format [45 CFR 46.102(m)].

INTRODUCTION

Ohio University is committed to expanding and disseminating knowledge for the benefit of the people of Ohio and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research subjects.

Human subjects are partners and participants in research and a precious resource to the University. At Ohio University, conducting human subject research is a privilege, not a right. Consistent with that philosophy, it is the mission of the Ohio University Human Subjects Research Protection Program to provide that:

1. the rights and welfare of human subjects are paramount in the research process;
2. the highest standards of ethical conduct are employed in all human subjects research;
3. research investigators are properly trained in the ethical and regulatory aspects of research with

human subjects;

4. research investigators deal honestly and fairly with human subjects, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
5. research using human subjects at Ohio University conforms with all applicable local, state and federal laws and regulations and the officially adopted policies of the University.

This document has been authored to assist members of the University community in fulfilling the stated mission of human subject research. This document is intended for the use of the Institutional Review Boards (IRBs) at Ohio University. This manual is directed to IRB chairs and members, the staff of the Office of Research Compliance (ORC) and other affiliated persons, and includes policies and procedures applicable to these persons in their capacities with the IRB.

PRINCIPLES, ROLES, RESPONSIBILITIES

1.0 Ethical and Regulatory Mandates for the Protection of the Ohio University Human Research Subjects Protection Program

The regulation of human subjects research by the U.S. Department of Health and Human Services is codified in 45 CFR 46. Because Subpart A of 45 CFR 46 has been adopted for human subjects research by many federal agencies it is known as the “Common Rule.” The Common Rule requires that every institution performing federally supported human subjects research file an assurance of protection for human subjects. This research should be guided by the ethical principles espoused in the Nuremberg Code and the Declaration of Helsinki and, additionally, should conform to the guidance documents described below:

1.1 The Belmont Report

The Belmont Report elucidates three ethical principles that should guide research:

- Respect for persons (applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations);
- Beneficence (applied by weighing risks and benefits);
- Justice (applied by the equitable selection of subjects).

The Belmont Report is attached to this document as Appendix A.

1.2 45 CFR 46

This regulation, published by the Department of Health and Human Services, codifies basic human subject protection measures. 45 CFR 46 is attached to this document as Appendix B.

1.3 21 CFR 50 and 21 CFR 56

These FDA Regulations define consent requirements for the use of certain types of drugs in human subjects research. 21 CFR 50 is attached to this document as Appendix C. 21 CFR 56 is attached to this document as Appendix D.

1.4 Assurance and IRB registration process

Ohio University, as an institution involved in biomedical or behavioral research, should have in place a set of principles and guidelines that govern the institution, its faculty, and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution, regardless of the source of funding. Assurances applicable to federally supported or conducted research must, at a minimum, contain such a statement of principles, which may include an appropriate existing code, declaration, and/or statement of ethical principles as formulated by the institution. The *Belmont Report* serves as such a document for Ohio University.

The *IRB Guidelines* represents the written procedures and guidelines provided for in Ohio University's Assurance.

References:

Declaration of Helsinki
The Belmont Report

2.0 Roles in the protection of human research subjects at Ohio University

2.1 The Institutional Official

The Institutional Official at Ohio University, as designated by the President of the University, is the Vice President for Research/Creative Activity.

It is the responsibility of the Institutional Official to oversee the University's compliance with federal regulations pertinent to human subjects research. The official document pledging this responsibility is called the Federalwide Assurance (FWA), approved by the Office of Human Research Protections (OHRP) at DHHS. The Institutional Official shall be responsible for all required institutional reports to sponsors and federal agencies.

Part of this assurance includes the development and adoption of policies and procedures for conducting human subjects research and the appointment of an institutional official to oversee this process.

2.2 Office of Research Compliance (ORC)

The Office of Research Compliance (ORC) is the chief administrative office of the Ohio University Human Subjects Research Protection Program. This office administers, supports, guides and oversees the work of the Ohio University Institutional Review Boards (IRBs) to uphold ethical and regulatory standards and practices in human subjects research at Ohio University. The Office of Research Compliance reports to the Institutional Official for human subjects protection issues and administrative matters. Recognizing the importance of uniting administrative support with human research subjects protection, the University has appointed the Vice President for Research/Creative Activity to serve as Institutional Official. As part of the Federalwide Assurance process, an institution is asked to identify a "Human Protections Administrator" (HPA) to serve as the primary institutional contact person for the Office for Human Research Protections. The University has designated the Associate Director of ORC to be the University's HPA.

2.3 Institutional Review Boards (IRBs)

The IRBs are established by the University and fall under the auspices of Ohio University. Each IRB is an appropriately constituted group (see 4.0 below) that the University has designated to review and monitor research involving human subjects. The University's IRBs are panels with expertise required for the review of the University's widely varied human subjects research studies.

2.4 Research Team Members

Every member of the research team is responsible for protecting human subjects in accordance with the guidelines specified in 1.0, and for complying with all IRB findings, determinations and requirements. Any team member who will have contact with human subjects or access to identifiable data must be listed as a member of the study team and complete human subjects research training as required.

2.4.1 Primary Investigator (PI)

The primary investigator is the individual responsible for the implementation of research, and, as such, must personally conduct or supervise the research. The PI is responsible for ensuring that the research study is accurately and completely submitted for IRB review, that IRB approval is obtained prior to initiation of research and before making any changes or additions to the research; that the IRB is informed of all changes in information previously presented to the IRB; that progress reports are submitted to the IRB as required; and that all unanticipated problems or serious adverse events involving risk to human subjects are reported to the IRB promptly. The PI is also responsible for ensuring that all members of the research team comply with the findings, determinations, and requirements of the IRB, including adequate performance of the informed consent process.

The role of PI implies administrative and fiscal responsibility as well as sufficient expertise for the research study. Though a trainee or another person may have primary responsibility for the intellectual content and may perform the research activities within the project, and, additionally, may garner primary credit for any publication resulting from the research, the PI has ultimate administrative and fiscal responsibility for the project, subject to University review and oversight. In cases where the primary investigator is a student, the advisor assumes the primary responsibility for ethical conduct of the study. This includes maintenance of research records following the student's graduation.

For information regarding the requirements to serve as a Primary Investigator, please refer to the section titled, "Principal (Primary) Investigator Status Appointments for IRB" within Section 28 of the IRB Policy/Procedure Guidelines, titled "IRB Guidance for Collaborating Individual Investigators."

2.4.2 Co-Investigator (Co-I)

Co-Investigators assist the PI in contributing to the scientific development or conduct of a project in a substantive, measureable way.

2.4.3 Research Assistant

A research assistant has a specialized, more defined role in the study, with a less substantive contribution to the scientific development or conduct of the project.

2.4.4 Advisor

In cases where the primary investigator is a student, an advisor must be part of the research team. The advisor, instead of the PI, assumes the primary responsibility of the study. The advisor must be an Ohio University faculty member, with a faculty email address. In general, an individual must meet the requirements to be a Primary Investigator in order to serve as an advisor. For information regarding the requirements to serve as a Primary Investigator, please refer to the section titled, "Principal (Primary) Investigator Status Appointments for IRB" within Section 28 of the IRB Policy/Procedure Guidelines, titled "IRB Guidance for Collaborating Individual Investigators."

2.4.5 Corresponding Investigator (CI)

The Corresponding Investigator is either the primary investigator, a co-investigator, or advisor. The CI serves as the liaison between the research team and the Office of Research Compliance, and represents the research team in all decision-making by solely responding to questions, submitting revisions, withdrawing proposals, etc., on behalf of the team. The research team can change who serves as the CI at any time, prior to or after approval. Research assistants and external investigators cannot serve as the CI.

2.5 Research team members who are external to Ohio University

If a PI wishes to add members to the study team who are not Ohio University faculty, staff or students, they have two options. The first option is for the PI to verify and provide assurance that the external investigator is affiliated with an institution with an active Federalwide Assurance (FWA) and that the external investigator has checked with that institution regarding IRB review requirements. The second option is that the PI completes the process to have Ohio University's FWA extended to cover the unaffiliated investigator. Requirements for this option are defined in the Ohio University IRB Guidance for Collaborating Individual Investigators.

2.6 Other University reviewers

In addition to Ohio University IRB review, Ohio University human subjects research studies may be reviewed by other University committees and individuals charged with responsibility for evaluation of specific component research compliance issues. These may include one or more of the following:

- Conflict of Interest committee
- Institutional Biosafety Committee
- Radiation Safety Committee and Environmental Health and Safety (EHS) personnel
- Institutional Privacy and Security Officers
- Health Insurance Portability and Accountability (HIPAA) Privacy Officers
- Contract and grant personnel in the Office of Research and Sponsored Programs
- Heritage College of Osteopathic Medicine (HCOM) research committee or members of the HCOM Research Office
- Data Safety Monitoring Board

- Department or school level review committees

The factual information, evaluations and recommendations of these research review units may be very useful to the IRB's consideration of the rights and welfare of human subjects within the context of the specific Ohio University research study.

The Ohio University IRB retains final responsibility and authority to approve each Ohio University non-exempt research study that involves human subjects. Furthermore, research approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, university officials or actions of these committees cannot approve research if it has not been approved by an IRB.

See the organizational chart in Appendix I for a graphical description of roles and hierarchies in the Human Research Protection Program at Ohio University.

3.0 IRB Mission and Authority

3.1 Scope and purpose

The purpose of the Ohio University IRB is to protect the rights and welfare of human research subjects. To achieve this, the IRB must advise investigators in designing research projects in a manner to minimize potential harm to human subjects, review all planned research involving human subjects prior to initiation of the research, approve research that meets established criteria for protection of human subjects, and monitor approved research to ascertain that human subjects are indeed protected.

The IRB also informs and assists Ohio University and its researchers on ethical and procedural issues related to the use of human subjects in research; facilitates compliance with relevant regulations of the United States Government; and provides a framework suitable for continued support by Government agencies, private foundations and industry for research involving human subjects at Ohio University.

3.2 IRB responsibilities and authority

All human subjects research carried out at Ohio University or under its auspices must be reviewed and approved by the IRB or determined to be exempt by the IRB (or its designate) prior to the involvement of human subjects in research.

The Ohio University IRB reviews human subjects research: (1) sponsored by the University; or (2) conducted by or under the direction of any faculty, staff or student of the University in connection with his or her institutional responsibilities.

The IRB must conduct initial and continuing reviews of research and report the findings and actions to the investigator and the institution. These reviews include: the review of all research involving human subjects at a convened meeting of the IRB (except research meeting the criteria for exemption or evaluated in expedited review); the approval of research with the concurrence of the majority of IRB members present at the meeting; and the evaluation of proposed changes in approved research protocols. In addition:

- The IRB has responsibility for oversight of all human subjects research that is not exempt from IRB review;

- The IRB must protect the rights and welfare of subjects according to 45 CFR 46, 21 CFR 50, and 21 CFR 56, as applicable.
- The IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities;
- The IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator and the Institutional Official. The Institutional Official will determine whether or not the action should be reported to appropriate federal regulatory agencies. If such a report is required, the Institutional Official shall be responsible for all required institutional reports to sponsors and federal agencies.
- The IRB must report to the Institutional Official unanticipated problems involving risks to subjects and others or serious or continuing noncompliance by investigators. The Institutional Official shall be responsible for all required institutional reports to sponsors and federal agencies.

3.3 Agreements to provide IRB review of research conducted by unaffiliated investigators

Occasionally Ohio University may be asked to provide IRB review for investigators who are affiliated neither with Ohio University nor with another institution that has an IRB. Circumstances in which this arrangement might be considered would typically involve a study based at Ohio University in which the unaffiliated investigator is collaborating. It will generally not be considered appropriate to extend IRB oversight to research by unaffiliated investigators in which Ohio University is not otherwise engaged.

All requests for Ohio University to serve as the IRB of record for an unaffiliated investigator must be referred to the Director of the ORC. This referral should include an "Individual Investigator Agreement" based on the Ohio University approved template. In most instances this agreement will apply to a single research project; less often, to a defined group of studies involving the unaffiliated investigator. The Director of ORC, in consultation with the responsible IRB and the Institutional Official, as appropriate, will determine whether the University will agree to extend IRB oversight to the unaffiliated investigator. If the decision is that Ohio University will provide IRB oversight for the unaffiliated investigator, the Director of ORC will be responsible for executing the "Individual Investigator Agreement" documenting this arrangement, in accord with the relevant Ohio University signature delegation. The agreement will be filed with the paper copy of the protocol.

3.4 Agreements for deferral of IRB review from one FWA institution to another

On some occasions when two FWA institutions are engaged in the same research study, it may be appropriate for one institution to rely on the IRB of the second for review and continuing oversight of that research. Circumstances in which this arrangement might be considered would typically involve studies primarily based at one institution, with somewhat peripheral involvement by investigators at the other. It is most commonly used in conjunction with hospitals that belong to the Centers for Osteopathic Regional Education

(CORE) system that HCOM utilizes for student physician training. In effect, this constitutes a deferral of the right of review by the institution with lesser involvement, which retains responsibility for ensuring compliance with all IRB requirements.

In January of 2018 for NIH funded studies, and in January of 2020 for other federally funded studies, (1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

(i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

(ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

An "IRB Authorization Agreement" is the form of agreement executed between the institutions to document this delegation of IRB oversight. Ohio University may be either the institution deferring to another institution or the institution to which the IRB review is delegated. All requests for such delegations must be referred to the Director of the ORC. The Director of ORC, in consultation with the responsible IRB and the Institutional Official, as appropriate, will determine whether the University will agree to the deferral. If the decision is to agree to the IRB delegation, the Director of ORC will be responsible for executing the agreement, in accord with the relevant Ohio University signature delegation. Copies of this agreement will be filed with the collaborating institution and the ORC at Ohio University. For studies that are not federally funded, the two universities may elect to utilize a collaboration agreement instead of an authorization agreement. In instances where the Ohio University investigator is requesting that Ohio University defer to another IRB, the Ohio University investigator must also request a deferral in the LEO IRB system. Only when the deferral request has been approved can the Ohio University investigator participate in the projects. Deferral approvals from Ohio University must also be renewed when the IRB approval from the reviewing IRB is renewed. For more information, see section 17b in the IRB Policy/Procedure Guidelines, titled "Ohio University IRB Deferral Process."

Ohio University has elected to utilize an independent IRB, Western IRB; to review industry sponsored clinical trials. In general, externally sponsored clinical trials will be routed through WIRB, as well as any study where the OU IRB in conjunction with the ORC determines that WIRB review is required based on expertise needed by committee membership. WIRB agrees to assume IRB oversight responsibility for specifically assigned research studies and to perform IRB functions in compliance with applicable federal and state regulations for new research studies involving human subjects research to be conducted at Ohio University. WIRB's services shall include, but not be limited to: review approval or disapproval of new protocols; review approval, disapproval or

modification of consent forms; review approval or disapproval of the investigator(s); monitoring of adverse event reports; and maintenance of required IRB records pursuant to 21 CFR § 56.115 and 45 CFR § 46.115. WIRB shall conduct continuing review of new research studies appropriate to the degree of risk in such studies. WIRB agrees to conduct at least an annual review of each study in progress.

Ohio University will determine if there are any local context issues that must be addressed by Institution's internal IRB, and will refer such studies to an internal IRB rather than to WIRB. In keeping with the requirements of 21 CFR § 56.112, Ohio University cannot approve any research study that has been disapproved by WIRB. Ohio University may, however, disapprove any study approved by WIRB. Ohio University agrees to abide by the decisions of WIRB and shall use its best efforts to ensure that the clinical research performed by Ohio University shall be conducted in accordance with those decisions.

References:

21 CFR 50
21 CFR 56
45 CFR 46.102(d),(f)
45 CFR 46.103
45 CFR 46.109
45 CFR 46.109(d)
45 CFR 46.110
45 CFR 46.113
Declaration of Helsinki
The Belmont Report

IRB ORGANIZATION AND ADMINISTRATION

4.0 IRB Membership

4.1 IRB membership requirements

Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. Additionally, each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas, or seek expertise through consultants, as outlined in 45

CFR 46.107(e).

The standards described above represent *minimum* requirements, which the Ohio University IRB typically exceeds. The appropriate size of the IRB will be determined by the board itself in consultation with the Institutional Official (IO) and the Director of ORC and/or the HPA.

When a protocol involving prisoners is reviewed the IRB must include at least one member with appropriate background and experience to serve as an advocate for the prisoner population. The exception to this is when a proposal is reviewed by more than one Board, only one Board need satisfy this requirement.

4.2 Appointment of members

The Institutional Official appoints members to the IRB based upon the recommendation of the Director of the ORC and/or the HPA in consultation with the IRB chair.

The Deans/Directors, the ORC staff, and the IRB will typically identify prospective IRB members. The ORC will communicate with the potential appointee and review the nature and demands of IRB service with the candidate. If the candidate is willing to serve, they will review the proposed service with the relevant unit head. Upon agreement by all parties, the Institutional Official generates the official letter of appointment.

IRB members are appointed for a three-year term, which may be renewed. There is no limit to the number of times a term can be renewed.

4.3 Appointment of the chair

The Institutional Official appoints the IRB chair, based upon the recommendation of the Director of the ORC and/or the HPA in consultation with the outgoing IRB chair and the prospective chair's unit head.

Typically, but not necessarily, the IRB chair is selected from among sitting members of the IRB. The chair should be an individual with credibility and standing in the institution to command respect among the research community and the IRB, and one who is committed to the protection of human subjects in research. The IRB chairs are appointed for three year terms, which may be renewed.

4.4 Alternate members

Alternate members are occasionally appointed to the IRB. Additionally, a primary member of any IRB registered under the same IORG number may serve as an alternate for any comparably qualified member on any other IRB of that institution or organization. Each alternate IRB member who replaces a primary member at any given meeting should have the experience, expertise, background, professional competence, and knowledge comparable to that of the primary IRB member whom the alternate will replace.

4.5 Non-voting members

An IRB may recruit non-voting members from among the academic or administrative staff of Ohio University, whose knowledge or presence at the meetings of the IRB would aid the IRB in conducting its duties. These members may take part in all meetings of the IRB, participate in the discussions, and make recommendations, but they may not vote on the

decisions. Non-voting members are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of non-voting members.

4.6 Termination of appointment

Appointment to the IRB may be terminated before the expiration of the three-year term. The Institutional Official may remove an IRB member if the Institutional Official, in consultation with the IRB chair or other parties, determines that the member failed to perform member duties.

When an IRB member leaves the university, or is otherwise unable to serve, the IRB member may voluntarily terminate their appointment to the IRB. It is appropriate to give sufficient advance notice so that a replacement can be found.

4.7 Consultants

The Ohio University IRB may, at the discretion of the chair or its members, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. While these individuals may or may not attend meetings, they may not vote with the IRB. Consultants are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of consultants.

4.8 Confidentiality agreement

Upon appointment to the IRB or attendance at an IRB meeting, members (voting or otherwise), and/or staff will sign the confidentiality agreement attached as Appendix G. See 11.4.7 for information regarding attendance by guests. Consultants will, likewise be advised of confidentiality issues.

4.9 Orientation and training of IRB members

Once a potential new member to the IRB has been identified, he or she is encouraged to attend a meeting as an observer in order to learn about the workings of the IRB.

The new member will complete an IRB orientation, which consists of an informational session on practical matters with the IRB staff. In addition, the new member will receive reference materials, the IRB member handbook, and links to other published guidance.

4.10 Compensation of members

Affiliated IRB members generally are not provided monetary compensation for their service; however, unaffiliated members may receive a stipend.

Departments of IRB chairs may receive compensation in the form of salary support if their IRB duties are expected to constitute a significant percentage of their time. The amount of this support will be negotiated. IRB chairs may receive direct compensation.

All members may receive limited compensation (such as food, parking, etc.) in return for their service to the IRB.

4.11 Liability coverage for IRB Members

IRB members function as employees or agents of the Ohio University. As such their actions are covered by the Ohio University liability coverage if taken within the course and scope of their employment or agency. This means that they are covered when performing

within the course and scope of their IRB responsibilities.

Unaffiliated members of the IRB are also covered by Ohio University liability coverage when performing within the course and scope of their IRB service.

4.12 Member conflict of interest

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

Examples of such conflicts of interest could include: a member of the IRB who serves as an investigator on research under consideration by that IRB; or a member who holds a significant financial interest (as defined in the University's Policy on Conflicts of Interest and Commitment) in a sponsor or product under study.

References:

45 CFR 46.107

21 CFR 56.107

5.0 IRB Administrative Support

The IRB staff supports the function of the IRB at the direction and under the supervision of the Director of the Office of Research Compliance, who reports to the Vice President for Research/Creative Activity. The Associate Director of the Office of Research Compliance is responsible for directing and overseeing all IRB support functions and operations; training, supervising and evaluating IRB staff; and developing and implementing procedures to effect efficient document flow and maintenance of all IRB records. As described in 4.0, the Institutional Official will consult with the Director of ORC and/or the HPA for advice and recommendations when appointing IRB members and chairs.

5.1 Education and training of ORC staff

Staff members will initially receive orientation to IRB and office procedures. Further training is provided by working in close interaction with fellow staff members.

Staff members will be provided with continuing education opportunities and resources will be made available for them to attend regional or national human subject protection meetings, as deemed appropriate by the Director of ORC.

ORC staff members will have a variety of informative resources available to them. Staff members will be encouraged to obtain professional certification, such as the Certified IRB Professional (CIP) designation.

6.0 IRB Record Requirements

6.1 IRB Documentation

The IRB shall prepare and maintain adequate documentation of the IRB activities listed below. Some of this documentation may be subject to public perusal under the Ohio Sunshine Law; however, the Office of Legal Affairs will be consulted prior to responding to any request for public access to IRB records.

6.1.1 Documentation includes copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved consent documents, progress reports submitted by investigators, reports of injuries to subjects, and statements of significant new findings provided to human subjects. These documents may be in paper files and / or the electronic (LEO) system.

6.1.2 Documentation also includes records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in 45 CFR 46.109(f)(1). This documentation should include any activity occurring after initial approval, such as modifications, renewals, adverse and unanticipated event reports, deviations, and descriptions of amendments.

6.1.3 Documentation includes copies of all correspondence, including substantive email, among the IRB, ORC, and investigators.

6.1.4 Documentation includes a roster of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the University; for example: employee, not affiliated, paid or unpaid consultant. The IRB roster includes voting members, both regular and alternate, but it does not include non-voting members.

6.1.5 Documentation includes copies of the minutes of all convened IRB meetings (see 7.0: Meeting minutes).

6.1.6 Documentation includes written procedures that the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval, has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

6.1.7 Documentation includes written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

6.1.8 Documentation includes statements of significant new findings provided to subjects.

6.1.9 Documentation of the rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.

6.2 IRB Record Retention Requirements

The study-specific records detailed in 6.1.1-6.1.3, above, relating to research that is conducted shall be retained for at least 3 years after completion of the research. *Records detailed in 6.1.4-6.1.8 above, shall be retained for at least three years following their last effective date,

but may be retained indefinitely.

*For studies that have been exempted from continuing review, study-specific records shall be retained for at least three years after the exemption is granted.

Authorized persons shall be able to access records for inspection and copying at reasonable times and in a reasonable manner. Investigators may be required to follow different record retention policies depending on discipline specific requirements, research sponsorship, etc. Please see the guidance presented in section 22 of the IRB Policy and Procedures book, which is entitled "Office of Research Compliance (ORC) Guideline on Research Document Retention and Destruction for Human Subjects Research."

References:

45 CFR 46.115

21 CFR 56.115

7.0 Meeting minutes

IRB Meeting Minutes should be in sufficient detail to show the following:

7.1 Attendance at the meetings:

7.1.1 Names of members present

7.1.2 Names of members absent

7.1.3 Names of alternates attending in lieu of specified absent members

7.1.4 Names of consultants present

7.1.5 Names of investigators present

7.1.6 Names of guests present

7.2 Documentation of actions taken outside of convened meetings

7.2.1 Documentation that expedited reviews conducted outside the convened meeting were reported to IRB members. The information provided to members should include, at a minimum, the title, the PI of each study, and the approval date. This information may be filed as an attachment to the minutes.

7.3 Actions taken by the IRB

7.3.1 Actions taken by the IRB at a convened meeting as well as the vote on these actions, including the number of members voting for, against, and abstaining, and (if applicable) notation that any members with a conflict of interest (identified by name) were recused and were absent for the discussion and vote.

7.3.2 The approval period for projects approved by the IRB. In specifying an approval period of less than one year, the IRB may define the period either with a time interval or a research milestone. The minutes should clearly reflect any determination requiring a review more frequently than annually. The IRB minutes may state that all approval periods are one year unless otherwise noted.

- 7.3.3 The basis for requiring changes in or disapproving research (see section 7.4 below).
- 7.3.4 For each protocol in which changes are stipulated by the IRB, a determination of whether the changes represent minor modifications that do not require verification by the convened IRB (approved with stipulation), or whether they are significant, requiring convened IRB review (tabled).
- 7.3.5 A written summary of the discussion of controverted issues and their resolution.

7.4 IRB findings and determinations

The following are required findings and determinations, and must be noted in the minutes if they are not clear in the protocol form. Documentation for these findings may be found in the IRB application or related correspondence with the investigator.

- 7.4.1 Determination of the level of risk for human subjects in the research study.
- 7.4.2 Justification for waiver or alteration of informed consent [45 CFR 46.116(e) and (f)].
- 7.4.3 Justification for the waiver of the requirement for written documentation of consent; [45 CFR 46.117].
- 7.4.4 Justification for approval of research involving pregnant women, human fetuses and neonates [Subpart B].
- 7.4.5 Justification for approval of research involving prisoners [45 CFR 46.306].
- 7.4.6 Justification for approval of research involving children [45 CFR 46.404-407].
- 7.4.7 Justification for approval of research planned for an emergency setting [21 CFR 50.24].
- 7.4.8 Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons.

References:

21 CFR 50.24
21 CFR 56.115(a)(2)
45 CFR 46.115(a)(2)
45 CFR 46.103(b)(4)(ii)
45 CFR 46.116(e) and (f)
45 CFR 46 Subpart B
45 CFR 46.306
45 CFR 46.404-407

IRB RESEARCH EVALUATIONS, PROCEDURES, CRITERIA AND ACTIONS

8.0 Determination if a project constitutes human subjects research subject to Ohio University IRB review

The IRB has been charged with the responsibility for reviewing and monitoring human subjects research conducted under the auspices of Ohio University. Therefore, the first question with respect to IRB review of a project is a determination of whether the project fits this definition. In light of the mission to protect human subjects, the IRB should err on the side of conducting an IRB review when

the determination is not clear. The definitions of “research” and “human subjects” for this purpose are derived from federal research regulations. The criteria for “under the auspices of Ohio University” have been determined by the campus and may extend beyond what is required by federal regulations.

8.1 Is it research?

Federal Regulations define research as “a systematic investigation, including development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.” Activities that meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes [45 CFR 46.102(l)]. As described in the Belmont Report, “...the term 'research' designates an activity designed to test a hypothesis [and] permit conclusions to be drawn...” Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective.”

Thus, a key aspect of research is that there be a systematic design in advance, generally utilizing a scientific approach or protocol, for the defined purpose of contributing to generalizable knowledge. Research can encompass a wide variety of activities, including: experiments, observational studies, surveys, tests, and recordings. Studies assigned an Investigational New Drug (IND) number or an Investigational Device Exemption (IDE) by the FDA are by definition research that requires IRB review [21 CFR 56.103].

“Research” generally does not include (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

However, some of these activities may include or constitute research in circumstances where there is clear advance intent to contribute to generalizable knowledge with a scientific protocol. An intent to publish is one possible indication of an intent to contribute to generalizable knowledge.

8.2 Does it involve human subjects?

Federal regulations state (1) Human subject means a living individual about whom an

investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (2) Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (3) Interaction includes communication or interpersonal contact between investigator and subject. (4) 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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record). (5) Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (6) An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. Thus, approaches involving only existing records or human specimens or observations may still constitute human subjects research requiring IRB approval. The ORC, in consultation with the IRB chair, if necessary, will make this determination. Simple observational studies of public behavior (including television and internet chat rooms) do not involve human subjects as defined when there is no intervention or interaction and the behavior is not private. Also, studies based on data collected for non-research purposes may not constitute human subjects research if individual identity is not identifiable. Examples include programmatic data such as service statistics, school attendance data, crime statistics, or election returns. Studies based on data that are individually identifiable data but also are publicly available may not constitute human subjects research [45 CFR 46.102(e)(4)]; however, the term "publicly available" is intended to refer to record sets that are truly readily available to the broad public, such as death certificates.

8.3 Is it conducted under the auspices of Ohio University?

In the interests of protecting human subjects participating in research that is either under university auspices or would appear to be under university control, human subjects research that meets any of the following criteria will be subject to Ohio University IRB review and monitoring:

- The research is sponsored by Ohio University.
- The research is conducted or directed by any faculty, staff or student of the university in connection with their Ohio University responsibilities. This includes research experiences for HCOM students, even if not specifically required for a course. This determination is based on the fact that they are still covered by Ohio University malpractice insurance and receiving Ohio University benefits.

Accordingly, an IRB approval will no longer be in effect when the Primary Investigator is no longer under the auspices of Ohio University, e.g. graduate or depart from Ohio University.

References:

21 CFR 50.3(g)
21 CFR 56.102(e)
21 CFR 56.103
45 CFR 46.102(e)(4)
45 CFR 46.102(e)
45 CFR 46.102(l)

9.0 Applications for IRB review

9.1 New studies

All applications submitted for IRB review are screened in the ORC for completeness before being distributed to the IRB. New proposals are submitted to the ORC through the LEO electronic IRB system. A complete submission for IRB review includes, when applicable: a) Ohio University IRB Project Outline Form, b) Informed Consent document(s), c) recruitment materials, d) survey instruments, and e) other materials specific to the proposed study (e.g., grant application, investigator's brochure, and sponsor correspondence with a regulatory agency such as the FDA regarding test item risk). The IRB retains the discretion to accept materials prepared for review in another IRBs format.

If the application is incomplete or otherwise not fully prepared for review, it is returned to the investigator or a request is made for necessary changes or to provide additional information. The ORC or an IRB representative may contact the investigator by phone, email or through the LEO IRB submission system requesting clarification of protocol issues or revisions to consent document(s) prior to referral to the IRB.

9.2 Amendments or modifications

Amendments or modifications are changes to a previously approved study. Amendments or modifications are reviewed in the same way a new study is reviewed, which may be by the convened IRB or by expedited review, depending on how the changes affect the protocol.

For more information on amendments or modifications, see section 16.0, which is entitled Modifications.

9.3 Continuing review for renewal

Some approved research studies must be reviewed by the IRB at least once per year. For information on continuing review, see section 17.0, which is entitled Periodic Review for Renewal.

9.4 Process at ORC

The ORC will conduct an initial screening of all applications for completeness (according to the criteria listed in section 9.1 above) and make a preliminary determination of the level of review to be conducted. Investigators should be aware that the ultimate determination as to the type of review will be made by the IRB chair (see section 10.0 below) or a designee.

Once a complete submission has been received, it is assigned an IRB protocol number based on the review level selected by the research team. The number consists of a two digit year (calendar year in which the protocol was submitted), an alphabetic character that designates review level, F – full committee review, X – expedited review, E – Exempt Determination, N – determined to not require review, D – deferred, W – Western IRB, followed by a sequential number. This number remains with the study in the IRB records unless a change in review level is determined by the Office of Research Compliance or the IRB.

A periodic review cannot be submitted if an amendment has been created in the electronic system and is still pending review, and an amendment cannot be submitted if a periodic review has been created and is still pending review. However, a periodic review with an amendment can be created and submitted on one form.

If there is a problem and a research team wants to start over, the submission that is routing or “pending review” should be withdrawn. If the submission is in the creating mode, it should be deleted.

10.0 Determination of type of review

10.1 Levels of IRB review

The three levels described below are outlined in the federal regulations and utilized by Ohio University.

10.1.1 Convened IRB review

For a detailed description of this level of review, see section 11.0, which is entitled Review by convened IRB.

10.1.2 Expedited IRB review

For a detailed description of this level of review, see section 13.0, which is entitled Expedited review of research.

10.1.3 Exempt from continuing IRB review

For a detailed description of this level of review, see section 15.0, which is entitled Exemption from continuing review.

10.2 Determination of review type

In order to determine the level of review necessary, the chair or the chair’s designee screens the entire application and makes a determination as to whether the project constitutes human subjects research and, if so, the level of review required. All applications are assigned to be reviewed at a convened meeting unless (1) they meet the criteria for expedited review listed in section 13.0 or, (2) they meet the criteria for exempt review listed in section 15.0.

11.0 Review by convened IRB

11.1 Projects requiring review by convened IRB

Any study involving greater than minimal risk requires a review by the convened IRB.

11.2 Scheduling of meetings

Typically, the IRB will meet at least once a month on a regularly scheduled day with the exact frequency to be determined by workload. The meeting schedule and submission deadlines are published on the ORC website, www.ohio.edu/research/compliance.

Scheduled meetings may be cancelled by the chair due to a) insufficient number of applications requiring review at a convened meeting, b) inability to secure a quorum for attendance, or c) other reasons as may arise that make a scheduled meeting unnecessary or otherwise inappropriate.

11.3 Materials

11.3.1 Primary reviewers

The IRB may use a primary reviewer system in which one or more members are assigned to lead the review and present the protocol for discussion at the convened meeting. Primary reviewers will be assigned in advance of the meeting by the IRB chair or ORC staff.

Primary reviewers must have access to all submission materials described in section 9.1 prior to a convened meeting. Their review should take into consideration all of the factors described in section 24.0, which is entitled IRB Evaluation Criteria.

11.3.2 Other reviewers

Prior to a convened meeting, all IRB members without a conflict will be provided with detailed materials describing the research so that each member will be able to discuss the protocol at the meeting. At a minimum, the IRB members other than the primary reviewer(s) must have access to the consent documents and the IRB application summarizing the protocol in sufficient detail to support the review. In addition, the complete documentation will be available to all members for their review in the LEO electronic IRB system, both before and at the meeting.

11.3.3 Agenda

All members will receive an agenda for the meeting that includes a list of protocols under review as well as a report of studies that have been approved using the expedited review level since the last convened IRB meeting.

11.3.4 Minutes of previous meeting

All members will also receive a copy of the minutes from the previous meeting of the IRB, to be reviewed and accepted during the meeting.

11.3.5 Communications

All relevant communications transpire and will be provided in the LEO electronic IRB system, when possible. Email messages to and from the ORC personnel will be copied into paper files and / or uploaded into the electronic system as needed.

11.4 Conduct of the meeting

11.4.1 Role of the chair

The chair leads the meeting of the convened IRB. This includes calling the meeting to order, leading the IRB through the agenda, and calling for motions and votes. The chair should ensure that all members have an opportunity to express their opinions and concerns on the research under review. If the chair is absent from a convened meeting, another committee member will be asked to lead the meeting.

11.4.2 Role of primary reviewers

When the primary reviewer system is used, the primary reviewers for a given research protocol should make an evaluation of the protocol before the convened IRB meets and should present the protocol during the meeting. This presentation should include an overview of the project and the identification of major issues arising in the project.

11.4.3 Voting

In order for research to be approved, it shall receive the approval of a majority of the members present at the meeting. The voting process proceeds as follows: The chair may entertain a motion and a second that the IRB take a certain action regarding a given protocol. The actions the IRB may take are as follows: approval, approval with stipulated changes (conditional approval), table, or disapproval. For a thorough discussion of these options, see section 12.0, which is entitled IRB Actions following review by the convened IRB. After a motion has been made and seconded, there should be an opportunity for discussion before a vote is taken. Those members present for the vote will be counted as either voting for, against, or abstaining.

Members who are recused from the vote (e.g., due to conflict of interest) should physically leave the room, would not be counted in the aforementioned tally, and should be identified by name in the minutes. In the case of a virtually convened IRB meeting, members with a conflict of interest will be required to either exit the meeting or mute their speakers until they are alerted via chat or text message that they may rejoin the meeting.

11.4.4 Open meetings

The meetings of the Ohio University IRB are not subject to Ohio "Open Meeting" laws because the Ohio University IRB does not constitute "public bodies" within the meaning of the Open Meeting laws and pursuant to the relevant guidelines issued by the Ohio University Office of Legal Affairs.

11.4.5 Recusal of members with a conflict of interest

When an IRB member has a conflict of interest (see section 4.12, which is entitled Member conflict of interest) that requires recusal from the discussion of and voting on a particular protocol, that member should leave the meeting room for the duration of the discussion and vote, except as requested to address questions raised by other members. If the member's recusal causes a loss of quorum, the vote should be postponed to another meeting. For this reason, IRB members should notify ORC prior to the meeting if they have a conflict of interest related to a specific protocol slated for review at the meeting, and every effort should be made to ensure an adequate number of members are in attendance.

11.4.6 Attendance by investigators

Investigators may be invited, or may request to attend the portion of the IRB meeting at which their protocol is discussed. The investigator may answer questions raised by the IRB. The investigator should not be present for the final deliberation and vote on the

protocol.

11.4.7 Attendance by guests

The IRB may permit guests to attend a meeting, for example, in order for them to learn about the IRB process. Members should be alerted to the presence of guests and their reason for attending. Guests must sign the confidentiality agreement prior to the start of the meeting.

11.5 Teleconferencing/videoconferencing

In some cases, teleconferencing and/or videoconferencing may be necessary in order to have a quorum for a meeting, or to ensure that someone with a proper level of expertise reviews a protocol. When the IRB makes use of this technology, all other normal meeting requirements apply.

References:

21 CFR 56.108

45 CFR 46.108

“Guidance for Institutional Review Boards and Clinical Investigators 1998 Update: A Self Evaluation Checklist for IRBs”

12.0 IRB Actions following review by the convened IRB

12.1 Approval of research

In the case of an approval with no changes, the research may proceed once the PI receives documentation of IRB approval.

Unless otherwise specified, the approval period for research approved without changes is one year from the date of the meeting at which approval was granted.

12.2 Stipulated minor changes or clarifications required prior to approval

The IRB may determine that a study may be approved with stipulated minor changes or clarifications. Minor changes are those changes that do not involve potential for increased risk or decreased benefit to the human subjects.

For minor changes, the IRB Chair or designee must ensure that the PI makes the appropriate changes to the research protocol. Such changes must be clearly delineated at the convened meeting so that subsequent review requires simple verification of concurrence. The research may proceed after the required changes are verified and the designated reviewer approves the protocol.

The chair will typically be assigned responsibility for reviewing the changes to ensure that the stipulated changes are appropriately addressed, but may appoint a designee, or ask for additional input from other committee members. The application receives final approval when all required changes have been submitted and approved. If the research team does not meet the stipulations determined by the committee, the proposal will be reviewed at a subsequent meeting.

Unless otherwise specified, the approval period for research for which minor changes were

stipulated is one year from the date of the last convened meeting at which the protocol was reviewed.

12.3 Table

The term “table” is used to describe the situation in which an IRB determines that substantive changes must be made before approval may be granted. The PI’s response, including any amended materials, must be reviewed by the convened IRB.

Subject to IRB discretion, a proposal may be withdrawn if the PI does not respond to issues outlined for a tabled protocol within a reasonable amount of time. If the investigator wishes to conduct a study that has been withdrawn, the investigator must submit a new application, incorporating comments from the prior IRB review.

Unless otherwise specified, the approval period for research protocols that are tabled is one year from the date of the last convened meeting at which approval was granted or minor changes were stipulated.

12.4 Disapproval

If the IRB determines that the research cannot be conducted at Ohio University or by employees or agents of the University or otherwise under the auspices of the University, the project, as proposed, is disapproved and may not go forward.

Disapproval usually indicates that a proposal requires major changes not likely to be feasible without a complete reassessment of the protocol by the investigator and/or sponsor. A proposal can only be disapproved in a convened meeting of the IRB.

In some cases, the IRB may want to alert other IRBs of the disapproval.

12.5 Suspension and termination of research study by IRB

The chair of the IRB or the convened IRB may suspend a study at any time if it is determined that the study requires further review or evaluation. This determination may be made due to an adverse event, noncompliance or other danger to human subjects. Once a study has been suspended, the chair of the IRB or the convened IRB should review the study and either require changes to the protocol, allow the study to restart, or terminate the study.

Though the chair may suspend a study, only the convened IRB can make the decision to terminate a study.

When a study is suspended or terminated, the IRB must notify the Institutional Official. If the suspended or terminated study is externally funded, the IRB must also notify the Office of Research and Sponsored Programs. The Institutional Official is responsible for all required reports to federal agencies.

12.6 Notification of IRB actions

The IRB sends notification of actions taken to the PI. Summaries of actions taken will be provided to the Institutional Official and to the Director of the ORC in the form of meeting minutes. If revisions to new and continuing human subjects applications are required, correspondence is sent to the investigator detailing requests for revisions, clarification, or additional information as well as information regarding continuing review.

Notification of approvals, terminations and suspensions will be provided to individual offices when appropriate, for example, the Office of Research and Sponsored Programs for externally funded studies; the HCOM Research Office for HCOM based studies, etc.

12.7 Appeal of IRB decisions

Investigators may appeal IRB requirements for specific changes in the protocol and/or consent document(s). At the discretion of the chair, the investigator may make such an appeal in writing to the IRB via the LEO IRB system. At the IRB's discretion, the PI may be invited to the IRB meeting at which the appeal will be considered.

If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision.

Other university officials may, in certain cases, decide that a research study may not be conducted despite IRB approval. One example could be a circumstance in which a certain project or area of research is deemed to be inappropriate or underfunded. In the case of a decision by the IRB to disapprove, suspend, or terminate a project, only the Institutional Official may request that the IRB reevaluate a project because of procedural questions related to the IRB review. However, the IRB decision to disapprove, suspend, or terminate a project may not be reversed by any officer or agency of Ohio University, state government or federal government.

13.0 Expedited review of research

13.1 Expedited review

An IRB may use an expedited review procedure to review some or all of the research appearing in the list below and found by the reviewer(s) to involve no more than minimal risk, minor changes in previously approved research during the period for which approval is authorized, or research for which limited IRB review is a condition of exemption.

Under an expedited review procedure, the review may be carried out by the IRB chair or by one or more experienced reviewers from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review at a convened meeting at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas.

The IRB should keep members advised of research proposals that have been approved by expedited review by providing members with the title, the PI, and the approval date of each protocol. The minutes will include documentation that this information was provided. For each expedited study approved, the IRB files must contain documentation showing the specific permissible category or categories justifying the expedited review, the review and action taken by the IRB Chair or designated reviewer and any findings required under 45 CFR 46 or 21 CFR 50 or 56.

13.2 Types of research eligible for expedited review

The first requirement is that the research be determined to present no greater than minimal risk. The second requirement is that the only involvement of human subjects fits within

one or more of the following categories.

Category 1 Research on drugs for which an investigational new drug application (21 CFR 312) is not required or research on medical devices for which a) an investigational device exemption application (21 CFR 812) is not required or b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Category 2 Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, nonpregnant adults, who weigh at least 110 pounds. For these subjects, amounts drawn may not exceed 550 ml in an 8-week period and no more than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.

Category 3 Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at the 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.

Category 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.

Category 5 Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

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

Category 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.

Category 8 Continuing review of research previously approved by the convened IRB (a) where the research is permanently closed to the enrollment of new subjects, and all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis and report writing.

Category 9 Continuing review of research, not conducted under an investigational new drug application or an investigational device exemption where Category 2 through Category 7 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

References:

21 CFR 56.110

21 CFR 312

21 CFR 812

45 CFR 46.110

OHRP guidance on the Use of Expedited Review Procedures (August 11, 2003)

63 FR 60364-60367: "Categories of Research that may be reviewed by an Institutional Review Board (IRB) Through an Expedited Review" (November 9, 1998)

14.0 IRB Actions following expedited review

14.1 Approval of research

In the case of an approval with no changes, the research may proceed once the PI receives documentation of IRB approval.

14.2 Stipulated changes required prior to approval

The chair or designated reviewer may determine that the research may be approved after minor changes or clarifications are made. Questions and issues should be communicated to the investigator via the LEO electronic IRB system. The response should be reviewed by the IRB chair or designee, to ensure that the investigator has made the appropriate changes. The application receives final approval when all required changes have been submitted and approved.

If expedited review raises questions of a substantive nature, the protocol may be referred for review by the convened IRB.

14.3 Suspension or termination of research study by IRB

The chair of the IRB or the convened IRB may suspend a study at any time if one or the other party determines that the study requires further review or evaluation. This determination may be made due to an adverse event, deviation, noncompliance or other danger to human subjects. Once a study has been suspended, the chair of the IRB or the convened IRB should review the study and either require changes to the protocol, allow the study to restart, or terminate the study.

Though the chair may suspend a study, only the convened IRB can make the decision to terminate a study. See section 12.0, which is entitled IRB Actions following review by the convened IRB.

15.0 Exemption from Continuing IRB Review

15.1 Exemption

Certain types of human subjects research may be exempted from review by the IRB. However, if a study is inappropriately excluded from IRB review, the involved investigators and all research at the university may be put at considerable risk. Because of this, exemptions must be determined by the Office of Research Compliance, upon review of applications for exemption.

An investigator may not initiate research involving human subjects that the investigator believes is exempt until the investigator has received formal concurrence of this exempt determination from the ORC. Changes to exempted studies must be reviewed by the ORC, just as amendments to studies receiving expedited or convened IRB review. In some instances, changes to an exempted study may render it no longer exempt.

15.2 Categories for exemption from continuing review

Research activities involving human subjects may be exempted from IRB review if the research is determined to present no greater than minimal risk and the only involvement of human subjects fits within one or more of the following categories [45 CFR 46.104(d)]:

Category 1 Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Category 2 Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §11.111(a)(7).

Category 3 (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met: (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; (B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §11.111(a)(7). (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else. (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

Category 4 Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met: (i) The identifiable private information or identifiable biospecimens are publicly available; (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects; (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch

activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Category 5 Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

Category 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.

Category 7 Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §11.111(a)(8).

Category 8 Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

- (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §11.116(a)(1) through (4), (a)(6), and (d);
- (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §11.117;
- (iii) An IRB conducts a limited IRB review and makes the determination required by

§11.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and
(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

If information comes to the attention of the ORC suggesting that there are factors increasing the sensitivity and/or potential risk to human subjects in research that otherwise would appear to qualify for exemption under the criteria listed above, the ORC may, in its own sole judgment, deem the protocol to be subject to expedited or convened IRB review.

15.3 Application of Exemption Categories and Subparts B, C, and D

Use of the exemption categories for research subject to the requirements of subparts B, C, and D: Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) Subpart B. Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.

(2) Subpart C. The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

(3) Subpart D. The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

References:

21 CFR 56.104(d)
45 CFR Subparts B, C and D
45 CFR 46.401(b)

16.0 Modifications to previously approved projects

(Expedited and Convened Meeting)

16.1 Modifications to approved protocols

A modification is a change in an approved research protocol. Review and approval by the IRB is required before investigators can modify research protocols, except when necessary to eliminate apparent immediate hazards to the subjects. Any proposed change to a previously approved project must be submitted as an amendment to that project and may be reviewed by the expedited review procedure or by the convened IRB, depending on the original review level and/or the IRB member's assessment of associated risk. Minor changes in previously approved research may be approved by expedited review. Minor changes are those that do not significantly alter the risks/benefits balance.

Modifications in a study that might increase the risk to human subjects should be reviewed

by the convened IRB. If an amendment requires convened IRB review, the amendment is reviewed by the IRB, as described for initial or continuing review.

17.0 Periodic Review for Renewal

17.1 Periodic review

An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, except as described in 45 CFR 46.109(f). The IRB shall have authority to observe or have a third party observe the consent process and the research. IRB periodic review responsibilities include reviewing reports of any unanticipated problems that involve risk to research subjects or others. This information may be gathered through investigator or sponsor reports, by third party observations, or by IRB inquiries.

If a discrepancy in the reported number of participants enrolled occurs, the ORC will seek clarification with the primary investigator. Resolution may require ORC staff to review all signed consent forms.

For more information on SAE/UPs, see section 19.0.

17.2 Criteria for requiring review more often than annually

Intervals for continuing review, in the absence of problems, are typically set to one year. However, the IRB may determine that more frequent intervals are appropriate. The IRB shall consider the following factors in determining the criteria for studies requiring more frequent review:

- Nature, probability and magnitude of anticipated risks to subjects;
- Likely medical or psychological condition of the proposed subjects;
- Overall qualifications of the PI and other members of the research team;
- Specific experience of the PI and other members of the research team in conducting similar research;
- Nature and frequency of adverse events observed in similar research at this and other facilities;
- Vulnerability of the population being studied (this should be understood to include unfamiliarity with the language used on consent forms and other printed matter intended for subjects in the study);
- Other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a research milestone, e.g., number of subjects enrolled. The meeting minutes should clearly reflect any determination requiring a review more frequently than annually.

Similarly, the IRB can determine that research that does not require continuing review per 45 CFR 46.109(f) may be required to undergo continuing review. The IRB shall consider the following factors in determining the criteria for this continuing review requirement:

- Previous protocol deviations and / or adverse events for the specific study or members of the study team;
- Nature and frequency of adverse events observed in similar research at this and other facilities;
- Other factors that the IRB deems relevant.

Expedited studies that are approved on or after January 19, 2019 will be approved with a one year approval period. This will enhance the protection of research subjects and allow the Office of Research Compliance to adequately track approved, open studies, and to assure post approval monitoring is sufficient.

17.3 Reminders

The LEO electronic IRB system sends courtesy renewal notices 30 and 60 days prior to the expiration of a protocol approval. Ultimate responsibility for submitting the renewal request in a timely manner rests with the PI. If an application for renewal is not received from the PI by the expiration date, the study will be closed.

17.4 Submission of applications for periodic review

Periodic reviews are submitted via the LEO electronic IRB system. When an application for periodic review is received, the submission is checked by the ORC for completeness. If no clarifications are needed, the submission is forwarded to the IRB chair or the chair's designee for review.

The application for periodic review will include a progress report in which the PI describes the number of subjects enrolled, any problems that occurred during the prior approval period, and any changes being requested as a part of the current renewal. The approved protocol, including consent form(s) and debriefing form(s) is available for review in the LEO electronic IRB system.

The process for renewing a deferred study or a Western IRB study requires that you locate the study in the "Expiring Soon" tab in the LEO electronic IRB system and select "Renew" from the "Options" column. You then enter the new IRB expiration date, upload the new IRB approval document, and select "Review & Submit."

17.5 IRB processes unique to periodic review

Research approved previously by expedited review is considered eligible for expedited review at the time of its regular periodic review, if a determination has been made that continuing review is required. Projects that were initially reviewed by the convened IRB continue to receive the same type of review unless the IRB determines that the study meets the criteria for expedited review as described in Category 8 or 9 in section 13.2, which is entitled "Types of research eligible for expedited review."

Investigators are notified via the electronic system of the decision of the IRB and any changes required. Final approval is not granted until all required changes have been made, reviewed, and approved.

17.6 Lapsed studies

A lapsed study is one for which the approval period has expired prior to the renewal approval by the IRB. If the PI fails to submit the materials for continuing review within three months following the expiration date, it is no longer eligible for renewal.

Once a study has lapsed:

- All study-related activities must immediately cease except those necessary for the welfare of the human subjects, as determined by the IRB, on consultation with the PI.
- If the PI desires to continue a study that has lapsed for more than three months, then the PI must submit a new application for review by the IRB and must wait for IRB approval before resuming the research protocol.
- An approval lapse on a study is considered a protocol deviation. The PI is required to submit a deviation report within 72 hours of the study being re-approved.

18.0 Study Closure or Completion

Research studies can be deemed completed for a number of reasons, each requiring a different degree of IRB involvement. In some cases, the IRB must perform in a supervisory or disciplinary fashion and require that a study be ended. More often, however, the investigator or sponsor will close the study and the IRB's role will be more passive.

18.1 Voluntary completion by investigators

By submitting a periodic review with a study status of "Completed (no enrollment, no treatment/intervention, data has no identifiers," the researcher confirms that the study is finished and that researchers have no further interaction with subjects or their identifiable data. This includes the destruction of master code lists and recordings. After confirmation that all data is de-identified, the protocol will be closed via the LEO IRB system.

Once the protocol is closed, the researcher is no longer required to submit for periodic review /renewal. If the investigator wishes to enroll new subjects for the study, or otherwise engage human subjects in research, the investigator must submit a new protocol in the LEO electronic IRB system for IRB consideration. Therefore, a study should only be closed once the investigator is no longer enrolling new subjects, using research interventions on existing subjects, collecting data (including follow-up data), or performing any other tasks that were identified as part of the approved study. A study will not invariably be considered completed when it is closed to enrollment, as research-related procedures may still be continuing. The IRB, in consultation with the PI, may consider closing a study when active data analysis and publication pursuant to the approved study has ceased. Additional research projects using data acquired in the approved study may constitute new human subjects research studies subject to separate IRB review.

18.2 Termination of a study by the IRB

In cases of Serious Adverse Events (SAEs) or Unanticipated Problems (UPs) (see section 19.0), cases of researcher noncompliance (see section 22.0), or in cases of protocol violations (see section 23.0), the IRB may decide to suspend a study to ensure subject safety. Upon investigation of the problem prompting suspension of the study, the

convened IRB may decide that a study should be terminated. Following the vote of the IRB to terminate a study and the evaluation of any appeals made by the PI, the study will be classified as closed.

Though the chair may suspend a study, pending IRB review, only the convened IRB may vote to terminate a study.

18.3 Expiration of approval period

Once the approval period for a given study has expired prior to the renewal of approval by the IRB, it is considered a lapsed study and all research-related procedures must halt, except where doing so would jeopardize the welfare of the human subjects, as determined by the IRB, in consultation with the PI (see section 17.6). If the PI submits the materials for continuing review within three months following the expiration date, the IRB may conduct continuing review and reactivate the protocol, if approved. This reactivation establishes a new approval period that is not retroactive to the prior date of expiration. If the PI desires to continue a study that has lapsed for more than three months, then the PI must submit a new application for review by the IRB, and must wait for IRB approval before resuming the research protocol. The LEO electronic IRB system notifies investigators upon expiration of IRB approval.

An approval lapse on a study is considered a protocol deviation. The PI is required to submit a deviation report within 72 hours of the study being re-approved.

19.0 Adverse Events and Unanticipated Problems in Research

More guidance on reporting requirements is available from OHRP's "Unanticipated Problems Involving Risks & Adverse Events Guidance (2007)." January 15, 2007 (<http://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html>).

19.1 Definitions

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

19.1.2 "Serious Adverse Event" (SAE) is any adverse event that results in death, is life threatening, results in patient hospitalization or prolongation of existing hospitalization, results in a persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

19.1.3 "Unexpected" or "unanticipated" refers to adverse events or other problems in the research where the nature and/or severity are not consistent with the information already provided to the IRB, including the project outline form and consent form(s).

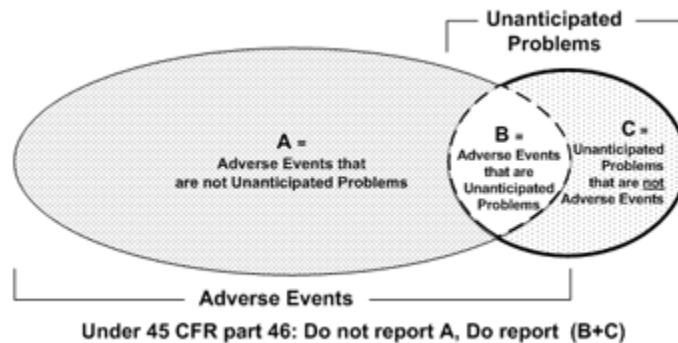
19.1.4 "Unanticipated Problems" (UPs) include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity or frequency);
2. related or possibly related to participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

19.2 UPs occurring at sites for which an Ohio University IRB has direct oversight responsibility

Upon becoming aware of an internal adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the definitions outlined in section 19.1. When an event is determined to represent an unanticipated problem, the PI is required to create and submit a report (see Section 19.4) to the IRB, using the Ohio University LEO electronic IRB system Event Report Form. This report is reviewed by one or more experienced IRB members (typically including the chair) and a decision is made as to whether or not the report should be presented and discussed at a convened meeting.

The following diagram was extracted from OHRP's "Guidance"



19.2.1 When an adverse event that is both serious and meets the criterion for an unanticipated problem and occurs at a site for which an Ohio University IRB has direct oversight responsibility, the PI must notify the IRB immediately upon discovery (within 72 hours) of the investigator becoming aware of the event.

19.2.2 Any other unanticipated problem should be reported to the IRB immediately upon discovery (within 72 hours) of the investigator becoming aware of the problem.

19.3 SAEs occurring at sites outside the jurisdiction of the Ohio University IRB

In multi-center studies, investigators are required to report adverse experiences that occur in subjects enrolled elsewhere (i.e., by non-University investigators) only when the adverse event is both serious and meets the criterion for an unanticipated problem. However, sponsors often require that adverse events that do not meet these criteria be reported to the IRB, and the investigator should do so. Documentation of such reports will be included in the LEO electronic IRB record after review by a chair or a designated individual. At the chair's discretion, review of these reports may be added as an agenda item at a convened meeting.

For multi-site studies in which a Data and Safety Monitoring Board (DSMB) is performing

aggregate analysis of adverse events, the IRB must receive a copy of the DSMB report.

19.4 Event Report

The event report submitted to the IRB must contain the following information:

- IRB study number
- Title of protocol
- Name of the primary investigator and relevant department, division or center.
- Subject identifier (study number/reference of subject)
- Date and site of event
- Description of event (nature of injury or other adverse occurrence, assessment of severity, and assessment of relationship to study)
- Handling/response to the event
- Any proposed changes in protocol or consent form due to event

19.5 Data and Safety Monitoring Plans (DSMPs)

The IRB or the research sponsor may require a research study to include a plan to ensure that relevant data are collected and assessed to monitor subject safety within the study. This plan is known as the data and safety monitoring plan (DSMP). Part of the DSMP may be the establishment of a data and safety monitoring board (DSMB), also sometimes called a “data monitoring committee” (DMC), to perform the evaluation procedures detailed in the DSMP. The group charged with implementing the DSMP—whether it is the research team, a DSMB or a DMC—must have adequate expertise to perform the analysis.

DSMBs for multi-site studies are responsible for forwarding summary reports of adverse events to each IRB involved in the study.

19.6 IRB responsibilities following receipt of Event report

The chair or a designated subcommittee of the IRB will review the event report and will decide whether the report should be presented and discussed at a convened meeting. The IRB chair will notify the Institutional Official and the event may be reviewed by the IRB at a convened meeting.

If an event poses serious risk to the safety of subjects or others, the chair or designated subcommittee may immediately suspend the study before presenting the report to the convened meeting. If the IRB suspends or terminates a study due to an event, it must notify the Institutional Official, who in turn is responsible for making any required reports to the appropriate federal regulatory agencies. In cases where the IRB is a central IRB, that central IRB will notify appropriate federal regulatory agencies. In cases where a researcher has IRB protocols approved by more than one Ohio University IRB, the chair of the other board will be consulted prior to action being taken that would affect protocols approved by the other board.

If this unanticipated problem is a death or serious injury, the ORC must notify the University’s Legal Affairs office immediately after it receives notification.

If the unanticipated problem involves a breach of confidentiality of data that is covered by the Health Insurance Portability and Accountability Act (HIPAA), the ORC will consult the University’s HIPAA Privacy Officer immediately after it receives notification.

It is the investigator's responsibility to make all required reports of adverse events to the FDA and/or sponsor. Investigators may have additional reporting responsibilities outlined in individual contracts that are not covered by this procedure.

References:

45 CFR 46.111(a)(6)

45 CFR 46.113

21 CFR 56.108(b)(1)

21 CFR 312.32

21 CFR 312.64 (b)

21 CFR 314.80

21 CFR 812.150 (a)(1)

Unanticipated Problems Involving Risks & Adverse Events Guidance, January 15, 2007

20.0 Emergency use of a test article

The FDA human subjects regulations allow for an investigational drug/device to be used in emergency situations without prior IRB approval. Emergency use is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval for the use. These are typically situations in which the intent is not to conduct research but to act in the best interest of an individual patient. Nevertheless, the FDA requires IRB involvement. The health care provider is still required to obtain informed consent under these circumstances. The emergency use must be reported to the IRB in writing within five working days.

The written report submitted to the IRB must include a cover letter explaining the medical condition, reason for use, and date administered as well as a copy of the signed informed consent document. The health care provider must also include any manufacturer information available on the product (e.g., drug brochure). Once the health care provider has provided written notice, the use is assigned an Ohio University IRB number, and the IRB chair or the chair's designee responds in writing that the information has been received. This acknowledgement of the IRB receipt does not constitute IRB approval.

Written informed consent must be obtained prior to administration or use unless the emergency situation makes it not feasible to obtain informed consent prior to using the test article. Exemption from the informed consent requirement is granted only when: (1) a life-threatening situation necessitates use of the test article; (2) the subject is unable to provide effective consent; (3) there is insufficient time in which to obtain consent from the subject's legal representative; and (4) there is no available alternative method of approved or generally recognized therapy of equal or greater likelihood of saving the subject's life.

The health care provider must document the infeasibility of obtaining consent as follows: The health care provider and a physician who is not participating in the clinical investigation must certify in writing the existence of all four conditions listed above before use of the test article. If in the health care provider's opinion immediate use of the test article is necessary to save the life of the subject and there is insufficient time to obtain the independent determination before using the test article, the health care provider is to make written determinations, then obtain the written review and independent evaluation of a physician who is not participating in the clinical investigation. The documentation of the

infeasibility of obtaining informed consent must be submitted to the IRB within five working days after the use of the test article. The IRB will respond to this report with an appropriate letter.

Although this procedure is designed to permit only a single emergency use of a test article for the treatment of one patient by one physician within the University, it is not intended to limit the authority of a physician to provide emergency care in a life-threatening situation. Should a situation arise that would require the emergency use of the test article for a second patient, by either the same or a second physician, subsequent emergency use should not be withheld for the purpose of gaining IRB approval. If it appears probable that similar emergencies will require subsequent use of the test article at the University, the health care provider should submit a protocol for future use of the article. The protocol must be prospectively reviewed and approved by the IRB before future use of the test article.

The use of a test article in a prospective investigation designed to be conducted under emergency conditions (e.g., emergency room research) does not qualify for the emergency use exemption. See section 21.0, which is entitled Exceptions from informed consent requirements for emergency research.

References:

FDA Information Sheets

21 CFR 56.104

21 CFR 56.312

21.0 Exceptions from informed consent requirements for emergency research

The conduct of planned research in life-threatening emergency situations where obtaining prospective informed consent has been waived, is addressed by 21 CFR 50.24 for research involving FDA regulated materials. In such situations, community notification and consultation are substituted for the consent of the individual subject. Because this raises serious ethical and legal questions, there is a set of additional requirements that must be followed and satisfied.

The research plan must be approved in advance by the FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are not eligible for the emergency use exception described in section 20.0, which is entitled Emergency use of a test article. Before approving a study of this nature, the IRB must obtain the concurrence of a licensed physician "who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation" [21 CFR 50.24(a)]. Because 21 CFR 50.24 permits an exception from the requirement for informed consent for a group of subjects, the case-by-case independent determination is replaced by the general concurrence of a licensed physician. Because the documented concurrence of the physician is required for approval of these studies, the IRB should ensure that meeting minutes specifically record this affirmative vote.

References:

21 CFR 50.24

October 2, 1996 Federal Register

FDA Information Sheet: Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update

22.0 Noncompliance of Researchers

22.1 Information regarding noncompliance

Information regarding noncompliance in human subjects studies may come to the attention of the IRB through several pathways. These include information contained in new applications, periodic reviews, adverse event reports, and reports from collaborators, employees, or subjects.

22.2 IRB investigations of noncompliance

The chair of the IRB reviews allegations of noncompliance. The chair makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the chair shall suspend the study procedures pending a timely investigation and institutional review and shall immediately notify the Institutional Official and the Director of the ORC, and at their discretion, the Office of Legal Affairs and the relevant dean and department chair or director. In cases where a researcher has IRB protocols approved by more than one Ohio University IRB, the chair of the other board will be consulted prior to action being taken that would affect protocols approved by the other board.

Investigations by the IRB focus on the protection of study subjects. In cases that involve allegations of scientific misconduct, the chair shall contact the Director of the Office of Research Compliance for further action. Inquiries or investigations into scientific misconduct do not preclude IRB review and actions.

The following are recommended procedures for resolving alleged noncompliance. These procedures should be used as a reference by the IRB chair and ORC staff as the noncompliance investigation is conducted.

22.2.1 Chronological sequence

- When made aware of a potential problem, ORC staff compiles information and presents concerns to the IRB chair.
- The chair determines whether to pursue the matter with the PI via the LEO system, telephone call, e-mail, paper memo, or in person. The purpose of such contact is fact-finding, i.e., to determine whether a problem exists and if so, its magnitude and significance relative to the rights and welfare of human subjects. The fact finding may be conducted by the ORC staff and reported to the IRB chair. The fact finding efforts may include, for example, consent form audits, research lab audits, and/or interviews with lab personnel and study participants.
- When the initial inquiry does not result in resolution of the matter, a meeting with the PI is scheduled as soon as possible. The purpose of the meeting may be to obtain additional information and provide the researcher an opportunity to explain why the noncompliance occurred.
- The IRB has the authority to suspend or terminate IRB approval of protocols that are found to be non-compliant with institutional policies and procedures, state laws, and/or federal laws or regulations. Other sanctions imposed by the IRB or the Office of Research Compliance may include but are not limited to additional training, compliance audits, letters of reprimand, and restrictions on serving as an investigator

on human subjects protocols.

- In cases where a researcher has IRB protocols approved by more than one Ohio University IRB, the chair of the other board will be consulted prior to action being taken that would affect protocols approved by the other board.
- If the IRB takes action regarding the noncompliance, the IRB sends written notification of these actions to the primary investigator and the Institutional Official. If the IRB's final action includes termination of the study or other sanctions, it also notifies the relevant dean and department chair or director. To the extent that any action includes suspension or termination in cases of externally funded programs, notice shall be sent to the Office of Research and Sponsored Programs.
- The IO is responsible for reporting noncompliance and the resulting IRB actions to the appropriate federal agencies, as applicable.

22.2.2 General guidance

- Care should be taken to maintain confidentiality when leaving messages for the PI via voice mail or with administrative and support staff.
- The chair or designee, should document in writing for the IRB files the outcome of any and all communications and discussions. Such documentation should be factual and objective and should include timelines for resolution (e.g., meeting dates, response deadlines).

23.0 Protocol Deviations and Violations

Protocol violations and deviations occur when there is a variance in a research study between the protocol that has been reviewed and approved by the IRB and the actual performance within the research study. A protocol violation or deviation may rise to the level of noncompliance (see section 22.0, which is entitled Noncompliance of Researchers). If any member of the research team or any other knowledgeable individual obtains information concerning deviations or violations, that individual is obligated to report this information to the IRB. The reporting of protocol deviations and violations is problematic because the working definition of what constitutes deviations and violations is variably understood and applied. Moreover, those obligated to file reports of deviations or violations with the IRB often have a personal interest in the research protocol on which the deviation or violation occurred.

23.1 Protocol Deviations

In any of the following cases, the variance in the research study should be considered a protocol deviation:

- The variance has no substantive effect on the risks to research participants.
- The variance has no substantive effect on the value of the data collected (i.e., the variance does not confound the scientific analysis of the results).
- The variance did not result from willful or knowing misconduct on the part of the investigator(s).

Some examples of protocol deviations are:

- Performing a planned procedure on a different timetable than previously specified in the research protocol because of an unforeseen disruption such as a subject's vacation.

- A mechanical failure (such as a recording device malfunctioning) that affects the protocol.

23.1.1 IRB notification and response in case of protocol deviations

Whenever a researcher anticipates the need to deviate from the procedures previously approved by the IRB, the researcher must obtain the approval of the IRB in advance. This is accomplished through an amendment.

When a deviation occurs without prior approval, the IRB must be notified promptly. The PI must create a Deviation Report and submit it via the LEO electronic IRB system within 72 hours of becoming aware of the deviation. The researcher will typically be advised to halt study activities until the deviation review is completed.

23.2 Protocol Violations

In any of the following cases, the variance in the research study should be considered a protocol violation:

- The variance has harmed or increased the risk of harm to one or more research participants.
- The variance has damaged the scientific integrity of the data collected for the study.
- There is evidence of willful or knowing misconduct on the part of the investigator(s).
- The investigator has demonstrated other serious or continuing noncompliance with federal, state, or local research regulations.

Some examples of protocol violations are:

- Enrolling subjects who do not fall within the range of exclusion/inclusion criteria established by the protocol without prior IRB approval.
- Adding, removing or modifying a research instrument (or adding to an existing instrument) in a survey study without prior IRB approval unless the changes are within a range of anticipated potential changes specified as acceptable within the IRB approval.

23.2.1 IRB notification and response in case of protocol violations

When the IRB receives notification of a protocol violation, the violation should be reviewed by the chair and/or designated members of the IRB. Violations may prompt the chair to suspend the study pending IRB review of the violation(s). In cases where a researcher has IRB protocols approved by more than one Ohio University IRB, the chair of the other board will be consulted prior to action being taken that would affect protocols approved by the other board.

24.0 IRB Evaluation Criteria

24.1 Risk

“Minimal risk” (for human subjects other than prisoners) means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of

themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [21 CFR 50.3(k), 21 CFR 56.102(i), 45 CFR 46.102(j)]

Risk should be considered in terms of both severity and probability, and should not be understood to include only physical risk, though such risks are important to consider. In reviewing a study, the IRB should also evaluate emotional and psychological risks, potential insurability risks, as well as risks to professional or community standing. For example, in conducting a drug use survey, respondents could face severe penalties in the workplace or in their community if confidentiality were breached even though the survey does not present a physical or psychological risk.

Risks to subjects must be minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and whenever appropriate, by relying on procedures already being performed on the subjects for diagnostic or treatment purposes.

Risks to subjects must be reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies or procedures subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

The IRB should be guided by the principles of The Belmont Report (Appendix A) in assessing risks to research subjects.

24.2 Benefit, including assessment of scientific/scholarly merit

In considering the possible benefit to be derived from a particular study, the IRB should examine both direct benefit to potential participants in the study (as may be the case in a drug study) as well as the long term societal benefits (i.e., generalizable knowledge) that the study may make possible.

The IRB is also charged with evaluating the scholarly merit of a project. Researchers who submit proposals deemed lacking in scholarly merit should be given feedback that will help the researcher to better define the scholarly significance of the project before resubmitting the proposal to the IRB. This evaluation of scholarly merit is an essential component of the IRB's risk and benefit assessment.

24.3 Selection of subjects

In accordance with The Belmont principles, both the burdens and benefits of research should be distributed equitably. Selection of subjects is one important means of ensuring this equity. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, mentally disabled persons, or economically or educationally disadvantaged persons. For more information, see 25.0, which is entitled Recruitment.

24.4 Review and documentation of informed consent

Unless specifically waived by the IRB, informed consent must be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116. See the discussion of informed consent in section 28.0.

24.5 Safety monitoring

When appropriate, the research plan should make adequate provision for monitoring the data collected to ensure the safety of subjects. See section 19.5, which is entitled Data and Safety Monitoring Plans.

24.6 Privacy of subjects and confidentiality of data

There should be adequate administrative, procedural and technical provisions to protect the privacy of subjects and to maintain the confidentiality of data. The assessment of adequacy should include consideration of the sensitivity of the data. Although there are some specific state and federal regulations governing privacy of some specific types of records (e.g., federal HIPAA, FERPA, state health care records privacy laws), privacy and confidentiality protections for human subjects do not derive merely from governmental regulation. They are also integral to the ethical principle of "respect for persons" as enunciated in The Belmont Report.

The NIH Data Sharing Policy and Implementation Guidance may be very helpful and is available at https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm, which discusses data protection in the course of exploring a variety of models for data sharing.

24.6.1 HIPAA

If human subjects research creates or uses individually identifiable health information that is "Protected Health Information" (PHI) as defined by the Health Insurance Portability and Accountability Act ("HIPAA"), the research use of that protected health information will require review from the Ohio University HIPAA Privacy Officer and may require additional IRB review and documentation (see section 29.0, which is entitled HIPAA and IRB Review).

24.6.2 FERPA

FERPA, or the Family Educational Rights and Privacy Act, which was established in 1974, often has to be considered when planning to conduct research involving the use of educational records. While FERPA seeks to provide parents or students with the rights to inspect files and request the correction of information they feel to be incorrect, the law also acts to ensure the privacy of such records. This guarantee of confidentiality of educational records often, by its very nature, has repercussions on those who wish to conduct research on educational practices.

While schools can release directory information without explicit consent, all other information is protected. Generally, any information outside of directory information may only be released with explicit, signed consent. Some, but not all, important exceptions to this rule when considering educational research are the following:

- School officials with legitimate educational interest
- Organizations conducting certain studies for or on behalf of the school

Many educators who are also researchers are surprised to find that the student records they personally hold (e.g., tests, journals, written assignments, etc.) are considered part of the official educational records of a student. Even more surprising is the fact that, when they are conducting research, they may not be considered to have a legitimate educational interest in the records they otherwise handle on a daily basis.

Those who wish to obtain data from educational records beyond directory information, for the purposes of research, are generally limited to three options:

1. The researcher may contact and obtain written consent for each individual whose records will be accessed for research purposes;
2. A school official with legitimate access (other than the researcher) may strip the records of any identifying information and provide the data to the researcher; or
3. The holder of the record may invoke an exception to FERPA in order to release the records to the researcher.

The assistance of Clemson University is acknowledged for language in this section.

Additional information on FERPA may be found at the website of the Department of Education at <http://www.ed.gov/policy/gen/guid/fpco/ferpa>. The specific language of the Family Educational Rights and Privacy Act can be found at <https://www2.ed.gov/policy/gen/guid/fpco/ferpa/index.html>.

Questions about FERPA and permissible uses of education records may be directed to the Office of Legal Affairs.

24.6.3 Certificates of Confidentiality

The Public Health Service Act at 301(d), 42 U.S.C. 241(d) authorizes HHS agencies to issue Certificates of Confidentiality in response to an application submitted to the agency by the investigator. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for human subjects. The Certificate of Confidentiality is intended to allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. This protection is not limited to federally supported research.

The IRB should be aware that the Certificate of Confidentiality has not been adequately tested in the courts and thus cannot be relied upon as an absolute guarantee of protection. The IRB should also be aware that the agency granting the Certificate of Confidentiality may require specific related language in the informed consent document. More information is available from HHS program officers and at the following electronic sites: <http://www.hhs.gov/ohrp/policy/certconf.html> and also at

<https://grants.nih.gov/policy/humansubjects/coc/what-is.htm>.

24.6.4 Limits on Confidentiality: Reporting Requirements

A primary investigator or other researcher may encounter in a research participant a dependency, abuse or neglect situation or a specific disease condition that is required to be reported to a state or local official. Such reporting requirements should be disclosed to subjects in the informed consent process. Generally, these reporting requirements are related to whether the participant is within a protected category—based on age or mental or physical condition—or if the condition may threaten the public health.

24.6.5 Limits of Confidentiality: NIH Data Sharing Policy

Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why data sharing is not possible. In cases where human subjects privacy precludes or limits data sharing, that explanation will be required in the NIH application. The NIH Data Sharing Policy and Implementation Guidance is available at http://grants.nih.gov/grants/policy/data_sharing/.

24.6.6 Limits of Confidentiality: Subpoenas

All subpoenas for research data should be referred immediately to the Office of Legal Affairs for assistance. In the event of such a subpoena, the University may confer with the state Attorney General's office about contesting the subpoena but cannot guarantee that the subpoena will be contested successfully or at all.

24.6.7 Limits of Confidentiality: The Shelby Amendment

The Shelby Amendment (Public Law 105-277 signed October 21, 1998) provides that if federally supported research results are used by the federal government in developing "an agency action that has the force and effect of law" then the federal agency may be required to obtain the research data and make it available if requested under the Freedom of Information Act (FOIA, 5 U.S.C. 552(a)(4)(A)). The extent and format of research data that must be shared is not specified in the Shelby Amendment. In some instances, it has been narrowly interpreted to be limited to published data specifically cited in the promulgation of federal regulations. Seek assistance from the Office of Legal Affairs regarding any request for research data under the Shelby Amendment.

24.7 Additional safeguards for vulnerable subjects

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards must be included in the study to protect the rights and welfare of these subjects. See section 32.0, which is entitled Special Topics: Research Subject Groups.

24.8 Continuing review for renewal

The IRB should determine which studies require continuing review, and the time frame for such review based on the degree of risk. These criteria can be found in section 17.2.

24.9 Recruitment and payment

The IRB must consider the appropriateness of the methods for identifying, recruiting and

compensating subjects and potential research subjects.

For more information, see section 25.0, which is entitled Recruitment and section 26.0, which is entitled Recruitment incentives.

24.10 Compensation for injury

Ohio University will negotiate liability coverage with the sponsor of the research study on a case-by-case basis. The University itself does not provide such coverage. The IRB shall require that subjects are provided with accurate information about the availability of compensation and/or treatment for injury that is a result of participation in the research study.

24.11 Reviews of scientific proposal or contractual statement of work

The ORC shall review any supporting documents (for example, master protocols from outside sponsors, federal grant applications, statements of work, etc.) for congruence with the application approved by the IRB.

24.12 Required education and certification of investigators on human research ethics

Anyone who will come in contact with human subjects or have access to identifiable human subject data (faculty, staff or students) must receive the training described below, regardless of source of funding of research.

- Completion of an approved web-based training module on the ethical use of human subjects. At this time, Ohio University is accepting completion of the CITI training module, accessed through the ORC website. Upon researcher request, the ORC will evaluate other training courses for acceptability.

24.12.1 Documentation that all research team members have completed required training in human subjects research protection

Prior to IRB approval of the research study, the IRB must receive documentation of completed ethics training for all members of the study team.

24.12.2 Human subjects research ethics training for unaffiliated investigators

When the Ohio University IRB is serving as the IRB of record for investigators who are not faculty, staff or students of Ohio University when they conduct human subject research, they are nevertheless subject to all of the usual human protection requirements, including Ohio University training requirements. The investigator must complete Ohio University human subjects ethics training as described in section 24.12.

Generally the University recognizes training completed in satisfaction of requirements at other FWA institutions.

For situations in which the unaffiliated investigator has limited English-language skills, we recommend working closely with the Ohio University researcher to complete this requirement.

25.0 Recruitment

25.1 Advertisements

IRBs and investigators should be cognizant that advertising for or recruiting subjects is often the first step in the informed consent process. When advertising is to be used, IRBs must review the information contained in the advertisement, as well as the mode of its communication, to determine whether the procedure for recruiting subjects affords adequate protection. IRB review is necessary to ensure that the information is not misleading to subjects.

Recruitment materials must include the IRB protocol number and state clearly that the project is human subjects research conducted by an Ohio University researcher.

Recruitment materials may also include:

- the name and contact information of the investigator;
- the purpose of the research, and, in summary form, the eligibility criteria that will be used to admit subjects into the study;
- a straightforward and truthful description of the incentives to the subject for participation in the study (e.g., payment or compensation); The description of incentives should not be the most prominent part of the materials (e.g., in larger or bolded font);
- the location of the research and the person to contact for further information.

If a study involves investigational drugs or devices, no claims should be made, either explicitly or implicitly, that the drug or device is safe or effective for the purposes under investigation, or that the drug or device is in any way equivalent or superior to any other drug or device. Such representation would not only be misleading to subjects, but would also violate FDA regulations concerning the promotion of investigational drugs and investigational devices. The FDA specifically discourages the use of terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational and that its effectiveness has not been proven.

25.2 Direct Solicitation

Generally, researchers at Ohio University should avoid soliciting by direct appeal to students, employees or trainees in that researcher’s department or class in an effort to recruit subjects for a study. Such direct solicitation (which should be distinguished from the dissemination of information) takes place within a power dynamic that could be construed as coercive by the potential subjects being solicited. The IRB should evaluate the proposed method of recruitment, as it would be applied to students, employees or trainees to make sure that recruitment materials are not presented in a manner that could suggest that their decision regarding research participation could have an effect on their relationship with instructors, mentors or employers. See also section 32.9, which is entitled Employees, students or trainees as research subjects.

Describing opportunities to participate in research to individuals in a subject pool (for example, students registered for classes at Ohio University that require participation in human subjects research or an alternative activity, or volunteers or patients who have enrolled in research registries) is not considered inappropriate since the prospective subject’s inclusion in the subject pool implies the individual’s desire to be apprised of such opportunities.

25.2.1 “Dear Colleague” Letters

The use of email or campus mail to distribute “Dear Colleague” letters intended to solicit the help of professional peers in recruiting subjects must be reviewed by the IRB and will be considered on a case-by-case basis.

25.3 Requests from outside researchers to solicit on the Ohio University campus

When non-University researchers wish to solicit human subjects on the Ohio University campus, these researchers should first contact a University faculty sponsor as well as the Ohio University’s ORC, and Legal Affairs as needed. Review by Ohio University IRB is not required. See also section 25 of the ORC Policies and Procedures book, which is entitled “Office of Research Compliance guidance on external investigators interested in recruiting OU students, faculty, and staff.”

References:

45 CFR 46.111(a)(4)

FDA IRB Information Sheet: "Advertising For Study Subjects" (1989)

26.0 Recruitment incentives

26.1 Payments to research study subjects

Subjects may be paid for their participation in research. However, the IRB should review the amount and type of payment and the proposed method of disbursement in the context of the proposed subject population to ensure that undue influence is avoided. Rewards such as course credit or goods with local monetary value should be considered to be forms of payment to study participants.

Problems with undue influence might occur, for example, if the entire payment were to be contingent upon completion of a longitudinal study or if the payment were unusually large. The appropriate level of payment is contingent upon a variety of factors, including: the amount of inconvenience or time associated with participation, local economic and cultural factors, the socioeconomic status of prospective subjects and any other circumstance that may affect subjects’ ability to make a decision regarding their participation in the study.

Payment should not depend on the degree of risk or amount of discomfort associated with participation.

26.2 Finders fees, enrollment bonuses, etc.

To minimize inappropriate financial incentives in human subjects research, Ohio University research may not include payments of incentives for achievement of enrollment target numbers or meeting enrollment accrual timelines (“enrollment bonuses”). Also prohibited are finder’s or referral fees to colleagues who may identify or refer eligible subjects to a research study (e.g., a general practitioner sending patients to a specialist conducting a study).

Additionally, University employees may not accept gifts, payments or in-kind support (including but not limited to financial payments, gift certificates, books, conference attendance and payment of travel expenses) as inducements for performance in Ohio University research other than as expressly included in budgeted project costs in a

contract between the University and the research sponsor.

26.3 Lotteries, raffles and prize drawings

Occasionally, investigators who are not in a position to offer equal compensation to each research subject propose to substitute a drawing as an incentive. For example, an investigator with only \$200 to compensate 100 subjects might propose a drawing for two \$100 prizes rather than paying each subject \$2.00.

University research projects may not include distribution of prizes to the research subjects via chances purchased by the human subjects or obtained by them in exchange for something of value including money, human tissues or blood samples, etc. The terms used for these purchased chance distributions include “lottery” and “raffle.” The prohibition is pursuant to state law and university policy.

A prize distributed by chance where the chance is obtained merely by attendance at an event or completion of a task (sometimes called a “prize drawing”) and not by the payment of any fee, donation or other consideration is not prohibited by law or university policy.

Regardless of the terminology used, University research should generally not include distribution of incentives to human subjects by chance. This method may represent coercion or undue influence if the incentive is sufficiently valuable. Additionally, the distribution of incentives via chance represents an unequal distribution of the incentive and may be unfair to subjects who will ultimately receive nothing. Generally, rather than conducting a drawing, researchers should provide equitable incentives to each subject, even if such a practice diminishes the value of the incentive.

However, use of incentives structured as described above for “drawings” may be considered by the IRB on a case-by-case basis for research studies of minimal risk, if the proposed incentives do not have potential for coercion or undue influence and clearly are not distributed in exchange for valuable consideration such as blood or tissue samples. Use of incentives by chance may also be approved on a case-by-case basis when justification is provided that use is integral to the study design.

If such an incentive is approved for a given study, consent form language describing the incentive should avoid terms like “lottery” or “raffle.” Acceptable terminology might include a reference to a “drawing based on chance in which each subject has equal odds of receiving [the incentive].” An estimate of the odds of receiving the incentive must also be included in both the compensation section of the project outline form and the consent form, i.e., “You have a 1 in 100 chance of receiving [the incentive].”

References:

Ohio State law

27.0 Investigator Conflict of Interest

27.1 Investigator Conflict of Interest: Internal Disclosure Requirements

The University requires submission of an annual conflict of interest disclosure form by all

University faculty and non-faculty employees applying for funding, as well as disclosure throughout the year of changes that may either: (a) give rise to a potential conflict of interest; (b) eliminate a potential conflict previously disclosed; or (c) result in an affirmative answer to any question on the Annual Evaluation Form previously answered in the negative.

Approval of conflict of interest disclosures cannot be issued until the submitter has completed and successfully uploaded the CITI Conflict of Interest training completion report into the LEO IRB system.

In addition, the LEO IRB protocol form includes questions that probe for potential conflict of interest in relation to the specific study.

27.2 Investigator Conflict of Interest: University Review Coordination with IRB

When the Office of Research Compliance receives a conflict of interest form disclosing a significant financial interest in human subjects research, either in the annual evaluation process or through an updated conflict of interest disclosure, the Office of Research Compliance will immediately provide that information to the relevant Ohio University IRB, the applicable Dean or Director, and the University Conflict of Interest Committee.

The IRB, along with the applicable University conflict of interest reviewer will share any written evaluations of the conflict of interest and its resolution, including any conditions or management plans that are put in place regarding that conflict.

The IRB possesses the final authority as to whether human subjects research may in fact proceed. Approval of a conflict of interest management plan by a Dean or Director and the University Conflict of Interest Committee does not obligate an IRB to approve a proposed human subjects research activity.

27.3 Summary of University Policy on Conflict of Interest in Human Subjects Research

It is University policy that individuals conducting human subjects research have a paramount responsibility to ensure that any conflicting interests of the researchers do not compromise the welfare and rights of those human subjects. The University's Policy on Conflicts of Interest and Commitment includes a rebuttable presumption that an investigator may not conduct human subjects research that is related to a significant financial interest of the investigator or the investigator's immediate family, except in compelling circumstances. The analysis of whether the circumstances are compelling will depend in each case upon:

- the nature of the science
- the nature of the financial interest
- how closely the financial interest is related to the research
- the degree to which the interest may be affected by the research
- the degree of risk to the human subjects involved that is inherent in the research protocol
- the extent to which the investigator is uniquely qualified to perform a research study with important public benefit
- the extent to which the interest is amenable to effective oversight and management.

When the significant financial interest is directly related to the human subjects research and may be substantially affected by it, the risk is greatest and the bar must be high.

In instances where a conflict of interest involving human subjects research is allowed, it is essential that research subjects and other interested parties be informed of the conflict of interest. If an investigator is participating in a multi-center trial and has been allowed to conduct human subjects research while possessing a significant financial interest, that fact should be made known to the PI or sponsor by the coordinating center (seek guidance of the Office of Legal Affairs before disclosing specifics of any significant financial interest). Notification of research subjects falls within the purview of the applicable IRB, which will determine whether and how the conflict of interest should be disclosed to the relevant human research subjects. This may include a description in the consent form of the conflict of interest.

27.4 Compensation from Sponsors

To minimize inappropriate financial incentives in study sponsorship, project support in all University projects:

- Must be based on fair market value of services performed or actual cost;
- Must be expressly stated in a contract between the University and the research sponsor;
- May not be conditioned upon a particular research result or tied to successful research outcomes; and
- May not include payments or other incentives for achieving human subject enrollment target numbers or meeting target enrollment accrual timelines or identifying eligible human research subjects. See section 26.2, which is entitled Finders fees, enrollment bonuses, etc.

University employees may not accept gifts, payments, or in-kind support (including but not limited to financial payments, gift certificates, books, conference attendance and payment of travel expenses) as inducements for performance in a University Project other than as expressly included in budgeted project costs in a contract between the University and the research sponsor.

References:

Ohio University Policy on Conflicts of Interest and Commitment

28.0 Informed Consent

Informed consent is a process rather than merely a document. Any individual invited to participate in a research study should be given a description of the study that is clear and complete enough for the individual to judge whether she or he wants to participate. The informed consent process should be designed to provide potential subjects with readily understandable information in an amount and timing appropriate to the level of risk in participating.

The subject's consent must follow and not precede receipt of this information unless the IRB approves a waiver or alteration of informed consent (as in some behavioral research that would be compromised by full disclosure in advance). Consent must be obtained from each subject who is legally, mentally,

and physically able to provide it unless waived by the IRB. Consent should be in writing unless the IRB finds that written documentation of informed consent may be waived. Consent forms and other informational documents should be written in simple language so as to be easily understood by persons with no technical background in the field. Except for broad consent obtained in accordance with 45 CFR 46.116(d):

- (i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.
- (ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

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

The standard expectation is that all subjects will sign a document containing all the elements of informed consent, as specified in the federal regulations and noted below. Some or all of the elements of consent, including signatures, may be waived under certain circumstances.

28.1 Basic Elements of Informed Consent

Unless the IRB approves exceptions, the following information must be provided to the subject when seeking informed consent:

- 28.1.1 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 that are experimental;
- 28.1.2 A description of any reasonably foreseeable risks or discomforts to the subject;
- 28.1.3 A description of any benefits to the subject or to others that may be reasonably expected from the research;
- 28.1.4 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- 28.1.5 A statement describing the extent, if any, to which confidentiality of the records identifying the subject will be maintained; (see section 29.0, which is entitled HIPAA and IRB Review and section 24.6, which is entitled Privacy of subjects and confidentiality of data)
- 28.1.6 For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
- 28.1.7 An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research related injury to the subject, if relevant. Typically, questions concerning a research

project should be referred to the PI for that project, whereas questions concerning the rights of human subjects should be referred to the Office of Research Compliance.

28.1.8 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.

28.1.9 One of the following “Future Use Statements” for any research that involves the collection of identifiable private information or identifiable biospecimens:

- (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
- (ii) A statement that the subject’s information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

28.1.10 The study title, names of researchers, and IRB protocol number.

28.2 Additional Elements of Informed Consent

For some studies, one or more of the following elements or information may be appropriate and required by the IRB:

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

28.2.2 Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent;

28.2.3 Any additional costs to the subject that may result from participation in the research;

28.2.4 The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject (particularly when potentially therapeutic experimental interventions are being administered and unscheduled cessation of the intervention may pose health risks to subjects);

28.2.5 A statement that significant new findings developed during the course of the research that may relate to the subject’s willingness to continue participation will be provided to the subject;

28.2.6 The approximate number of subjects involved in the study.

28.2.7 A statement that the subject’s biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

28.2.8 A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

28.2.9 For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

28.3 Elements of Broad Consent

Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted as an alternative to the informed consent requirements in sections 28.1 and 28.2. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

- 28.3.1 The information required in paragraphs 28.1.2, 28.1.3, 28.1.5, and 28.1.8 and, when appropriate, 28.2.7 and 28.2.9 of this section;
- 28.3.2 A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- 28.3.3 A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- 28.3.4 A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- 28.3.5 Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
- 28.3.6 Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and
- 28.3.7 An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

28.4 Exceptions to informed consent requirements for research involving public benefit programs

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB satisfies the requirements of section 28.4.1 of this document. If a broad consent is used, an IRB may not omit or alter any of the elements required in section 28.3.

- 28.4.1 The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

Public benefit of service programs; [45 CFR 46.116(e)(3)(i)(A)]

Procedures for obtaining benefits or services under those programs; [45 CFR

46.116(e)(3)(i)(B)]

Possible changes in or alternatives to those programs or procedures; or [45 CFR 46.116(e)(3)(i)(C)]

Possible changes in methods or levels of payment for benefits or services under those programs; [45 CFR 46.116(e)(3)(i)(D)] and

The research could not practicably be carried out without the waiver or alteration. [45 CFR 46.116(e)(3)(ii)]

For research using protected health information, see also section 29.3, for additional criteria for waiver or modification of HIPAA requirement for written authorization.

28.5 General exceptions to informed consent requirements 45 CFR 46.116(f)

An IRB may approve a consent procedure, that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent, provided the IRB satisfies the requirements of section 28.5.1 through 28.5.5 of this document. If a broad consent is used, an IRB may not omit or alter any of the elements required in section 28.3.

28.5.1 The research involves no more than minimal risk to the subjects; [45 CFR 46.116(f)(3)(i)]

28.5.2 The waiver or alteration will not adversely affect the rights and welfare of the subjects; [45 CFR 46.116(f)(3)(iv)]

28.5.3 The research could not practicably be carried out without the waiver or alteration; [45 CFR 46.116(f)(3)(ii)]

28.5.4 Whenever appropriate, the subjects will be provided with additional pertinent information after participation; and

28.5.5. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

For research using protected health information, see also section 29.3, for additional criteria for waiver or modification of HIPAA requirement for written authorization.

28.6 Posting of clinical trial consent form

28.6.1 For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll human subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

28.6.2 If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g., confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

28.6.3 The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

28.7 Other information concerning informed consent

28.7.1 The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order for informed consent to be legally effective.

28.7.2 Nothing in this policy is intended to 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 law.

28.8 Short form consent procedures

There may be circumstances when a subject is unable to read the full consent document (e.g., when the subject is illiterate or does not speak the language in which the consent document is written). In most circumstances, the IRB expects that a translation of the full form will be provided. However, there may be times when there is no opportunity to prepare a long form in advance; in such cases, a short form may be used.

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

28.9 Waiver of written consent

The IRB may waive the requirement for the investigator to obtain a signed consent form in cases where circumstances warrant such a waiver. Such a waiver is allowable if:

- The consent document is the only link between the subject and the research and the principal risk of harm would come from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or [45 CFR 46.117(c)(1)]
- The research presents no more than a minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context. [45 CFR 46.117(c)(2)]

In lieu of a signed consent form the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research in the form of an information or fact sheet. This statement should contain, at a minimum:

- A statement verifying that the project involves research;
- A description of the level of involvement and amount of time expected from subjects;
- A description of the study;
- A description of the risks and benefits to subjects;
- A statement describing the subject's rights;

- A description of the compensation to be provided to subjects;
- The IRB protocol number;
- Contact information for both the investigator and the IRB.

Examples of circumstances in which a waiver of written consent may be granted include situations where the researcher plans to use an abbreviated consent form, as in recruiting passersby for a brief, minimal risk, procedure. Similarly, a waiver may be granted to allow researchers to obtain oral consent for a survey of a passersby or a telephone survey. Finally, a waiver may also be granted if researchers wish for subjects to imply their consent by returning a survey via the mail or the internet. This last approach is especially useful in preserving the anonymity of the subjects surveyed. In situations when anonymity of subjects is an important concern, investigators should ensure that this anonymity is preserved in the process of compensating subjects for their participation (e.g., obtaining social security numbers for check requests, etc.).

For research using protected health information, see section 29.3, on the additional criteria for waiver or modification of HIPAA requirement for written authorization.

28.10 Ohio University Consent Form templates

In most cases the IRB requires that a Consent Form template (Appendix F) be used for all consent form documents. This consent template contains all of the basic elements described above. For clarity and to ensure timely processing by the IRB, the consent form should follow the guidelines described below.

The consent form and study fact sheet must be written at a level understandable to all potential participants and it must contain all information that would reasonably affect the subject's willingness to participate. In order to facilitate this requirement, the IRB will provide templates that reflect appropriate language for various subject populations. The consent form should be written in second person with "you" or "your child" consistently used to refer to the subject in all statements.

In most cases, the title of the project as listed on the consent form should be the same as the title listed on the application form, though the IRB may suggest or require modifications in the title under certain circumstances (e.g., in case the title would alert subjects to deception in the study or when the title may be too explicit regarding subject criteria as in a study of dysfunctional parents).

The date on which the consent form was prepared or modified should be indicated on the form, as illustrated in Appendix F, so that revised forms can be easily distinguished from prior versions.

28.11 Assent by children

Except under specific circumstances, assent to participate in a study must be obtained from minors (i.e., in Ohio, subjects aged 17 and under) who are capable of providing assent. The IRB shall determine that adequate provisions are made for soliciting the assent of the children (this includes providing age specific language to the prospective subjects), when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be

made for all children to be involved in research under a particular protocol, or for each child individually, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be assented or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children (such as in a study with therapeutic potential), and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116.

28.12 Parental permission

Unless otherwise provided by state law, or unless this requirement is waived by the IRB pursuant to 45 CFR 46.408(c), the permission of the parent or legal guardian is required in order for minors to participate in research.

Where research is covered by 45 CFR 46.406 and 46.407, permission is to be obtained from both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

In accordance with 45 CFR 46.408(c), in addition to the normal waiver requirements, the IRB may waive the parental permission requirement if it determines that a research protocol designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects. This waiver might apply to studies involving neglected or abused children, or older adolescents presenting in medical situations wherein a parental consent requirement might deter the child from seeking needed care (e.g., seeking care at an STD clinic). If parental permission is waived, the IRB must be sure that an appropriate mechanism for protecting the children is substituted. The choice of an appropriate mechanism would depend on the nature and purpose of activities in the protocol, the risk and benefit to the subject, and their age, maturity, status, and condition.

28.12.1 Durability of Parental Permission

Generally, if a subject whose participation was provided through parental permission reaches the age of majority while participating in the study, the informed consent of that subject should be required for continued participation in the study. The IRB may waive this requirement for informed consent if the criteria for such a waiver are met. See sections 28.3, 28.4 and 28.7.

28.13 Surrogate consent for subjects who are decisionally impaired

There is an important distinction between the legal meaning of the term “incompetent” and our broader use of the term “decisionally impaired.”

- “Incompetence” is a finding of a court of law that results in the appointment of a legally authorized representative for the individual judged incompetent by the court.
- Decisionally impaired persons are those who have a diminished capacity for

autonomous decision making due to a psychiatric, organic, developmental or other disorder that affects cognitive or emotional functions. Some adult individuals who appear to be decisionally impaired may not have been declared legally incompetent. For these individuals, there may not be a representative authorized under Ohio state law to consent to the individual's participation in research unless the individual had previously, while of sound mind, executed a power of attorney broad enough to include consent for the individual's research participation.

- Seek the guidance of University counsel if there are questions about legal authorization for surrogate consent in specific situations.
- See section 32.5, which is entitled Decisionally impaired subjects for more information on IRB review of their participation in research. See also section 24 of the ORC Policies and Procedures book, which is entitled "ORC Guideline on Impaired Capacity and Consent."

28.14 Obtaining consent from non-English speaking subjects

Researchers should take great care when they obtain informed consent from individuals who do not speak English or whose understanding of the language is limited. Researchers should be fluent in the subject's language or an interpreter should be available during the consent process and throughout the subject's participation, as needed. Consent forms should be prepared in the language understandable to potential subjects. For more information, see section 28.13.

When performing research using non-English speaking subjects, the use of short form consent documents should only be used when unexpected circumstances arise and there is not sufficient time to prepare a full consent form translation. The short form should not be used as a convenient way to circumvent translation of the full consent form. See section 28.6, for more information.

While the use of non-English speaking subjects presents a unique set of challenges for the researcher, care must be taken not to exclude non-English speaking subjects from research that may have potential benefits.

28.15 Translation and informed consent

Attention should be paid to both oral interpretation and written translation in the informed consent process.

28.15.1 Oral interpretation

Oral interpretation should be performed by a qualified individual. The individual performing the interpretation should be available for ongoing communication between subjects and investigators.

28.15.2 Written translation

Written translation of informed consent documents should be performed by a qualified individual. Though there is no standard definition of what constitutes a "qualified individual," the investigator should demonstrate due diligence in obtaining an adequate translation of the informed consent documents from an individual whose qualifications would appear adequate to a reasonable person. Back translations to English may be one method for validating the accuracy of the translation; however, back translations are not

always sensitive to dialect and idiom.

28.16 Consent for use of stored samples and genetic testing

In general, all anticipated uses of collected samples of human tissues, body fluids, or biological products should be carefully delineated in the consent form.

If genetic testing is to be done on the collected sample, the consent form should disclose the specific genetic information to be obtained, whether the information may be of value to the subject, whether and how that information will be disclosed or made available to the human subject and, if so, whether genetic counseling will be available.

- 28.16.1 If specimens are to be collected and stored for as yet unspecified purposes (genetic testing or otherwise), this should be addressed in the consent form or in an addendum. Generally, in cases where the primary purpose of the study is to store specimens, then an addendum is unnecessary. The addendum is required when specimen storage is adjunct to the main purpose of the study.

The consent form and process for maintaining human specimens in a repository for future research uses must inform the subjects explicitly about the unspecified possible future use of the specimens and related personal information. The consent process must include the following:

- The sample will be stored and possibly used in future research studies.
- A description of any personal information about the specimen source will be maintained (this may or may not include identifiers).
- If no personal identifiers will be used for labeling the stored samples, i.e., if it is impossible for the sample to be linked with the subject, the consent form should so state.
- If personal identifiers are to be used that will allow future matching of the subject to the collected sample, the consent form should describe how they will be used, how privacy and confidentiality will be protected, whether and under what circumstances identifying information would be disclosed.
- Future research using the samples will be reviewed by an IRB prior to additional use of the samples.
- Whether and how researchers may contact individuals whose specimens are in the repository.
- A statement about any potential commercialization and that there are no plans for subjects to share in financial proceeds that may accrue from products derived from the specimens.
- Whether and under what circumstance and how any results from research studies using the specimens would be communicated to or available to the human subjects, if, for example, the information gathered also applied to family members.
- If specimens are individually identifiable, how the specimens and associated data may be withdrawn from the repository. If the specimens are not individually identifiable, a statement that they may not be withdrawn for that reason.

28.17 Consent for inclusion in research registry

A research registry is a database of potential research subjects who have signaled their willingness to participate in research studies. Subjects must consent to inclusion in the registry. However, it is possible for researchers to use a staged consent process in which preliminary consent is granted by subjects when they are included in the registry and additional consent is obtained when those subjects participate in a study.

28.18 Verifying subject consent

Unless waived by the IRB, participants must sign and date the consent form prior to participation in the study. The signed consent form should be retained in the investigator's files and a copy of the consent form should be provided to the person giving consent.

28.19 Informed consent forms in health care records

An informed consent document for research participation is not a healthcare document and ordinarily would not be included in a health care record. Similarly, other forms of information about research interventions that are not health care would not ordinarily be included in an individual's health care record.

However, some clinical research includes health care. Additionally, information about some research interventions, whether or not treatment-related, may be relevant to a health care provider's diagnosis and treatment decisions about the individual. For example, it may be important for a health care provider not associated with the research study to know that a patient is receiving drugs or interventions as part of a research protocol. In these circumstances it may be appropriate for the consent form to be included in the health care record.

At the time of the review, the IRB, in consultation with the PI, should make a determination as to the appropriateness of including the consent form in the health care record. Conversely, there may be circumstances wherein it is inappropriate to include, and specific mechanisms should be in place to exclude research information from the health care record (e.g., when research participation is not relevant to ongoing health care but might disclose sensitive personal information such as sexual preferences). If the decision is made to include the consent form in the health care record, then the informed consent and HIPAA authorization for the study should state that this information will be placed in the health care record.

In determining whether research participation records will be placed in the health care record, IRBs and investigators should consider several points. Although protection of the subject's health and safety by providing research participation information to a healthcare provider is an appropriate concern, there are also other human subject's welfare issues to be considered, particularly privacy and confidentiality. Some human subjects will not want information about their research participation to be shared with their healthcare provider for a variety of reasons including personal privacy, concern that the information may be transmitted to a health insurer or employer, etc. These are the very privacy and confidentiality concerns that underlie the HIPAA regulations giving patients the right to know what is in their health care record and to control disclosure of their protected health information from the health care record.

28.20 Record retention of informed consent forms

As with all protocol related materials, a copy of the approved consent documents (not the signed consent forms themselves) must be retained by the IRB for a minimum of three (3) years following the end of the study. For more information on storage of records, see section 6.0, which is entitled IRB Record Requirements. See also section 22 of the IRB Policies and Procedures book, which is entitled “ORC Guidelines on Document Retention and Destruction.”

References:

45 CFR 46.116

45 CFR 46.117

45 CFR 46.404-408

29.0 HIPAA and IRB Review

“HIPAA” is the Health Insurance Portability and Accountability Act of 1996, which includes regulations that specifically address the use of “protected health information” in research (For a definition of “Protected Health Information” see the Definitions section.).

Ohio University is considered a ‘hybrid’ institution, because it performs activities that includes both covered and non-covered functions.

IRB protocols that check “Yes” to the question, “Does this project involve activities covered by the Health Insurance Portability and Accountability Act (HIPAA)?” are typically reviewed and approved by the Ohio University HIPAA Privacy Officer. This applies to new proposals, amendments, and periodic review submissions. In their initial review, the HIPAA Privacy Officer will make an official determination whether the research involves HIPAA-covered activities. This review typically takes place within 72 hours of submission. If it is determined that the research involves HIPAA-covered activities, the proposal will receive review and approval from the HIPAA Privacy Officer before an IRB approval is issued. In the absence of a HIPAA Privacy Officer, the IRB coordinator will send an email to the Director and Associate Director of Research Compliance. The email must summarize the HIPAA activities, letter of support, and board determination as well as any previous review by the HIPAA Privacy Officer. The Director will then authorize the IRB approval to proceed or direct the coordinator otherwise. This review and authorization does not constitute review by the HIPAA Privacy Officer.

HIPAA information privacy requirements are additional to ethical and regulatory protections for human research subjects and do not supersede them. The HIPAA privacy regulations are focused on privacy and security protections for individuals’ health care information that is termed “protected health information” (PHI). If a research study either uses or creates protected health information, HIPAA documentation requirements apply to those research uses of PHI in addition to relevant privacy and confidentiality protections that are required by ethics and federal regulation for human research subject protection.

Research use of PHI requires explicit authorization except under the following circumstances:

- The individually identifiable health information is not generated in the course of healthcare services by a health care provider, health plan, or health care clearinghouse and will not become part of a record applied to treatment, payment or

healthcare operations or

- The IRB has approved a waiver of authorization; or
- The data are “de-identified” before the data are provided to the researcher; or
- The data are converted to a “limited data set” before the data are provided to the researcher and the use of the “limited data set” is governed by a data use agreement that includes HIPAA-specific provisions; or
- The research is limited to decedents; or
(Note that while decedents are not included in the Common Rule definition of “human subjects,” the disclosure of their PHI by a covered entity is subject to HIPAA requirements.)

- The research is limited to a “review preparatory to research.”

Note that the Ohio University policy is that use of the “review preparatory to research” HIPAA option (a) is limited to preparation of a research protocol or assessment of feasibility of performing a specific research protocol; and (b) does not include recording any protected health information; and (c) may not be used to prescreen patients as part of the recruitment process. Once there is intent to recruit pursuant to a formulated protocol, then the research activity is sufficiently well prepared to require IRB approval.

Certain of these circumstances are the responsibility of the IRB to oversee, while others (for example, reviews preparatory to research) are not.

The Ohio University IRB will perform the following HIPAA review and approval responsibilities within the larger context of its responsibilities for the protection of human research participants that include review of privacy and confidentiality issues broader than those covered by HIPAA:

- Verification that all team members listed on a protocol involving HIPAA-protected activities have completed the required Information, Privacy, and Security CITI HIPAA training. Completion is required annually for this training.
- Review and approval of letters of support from covered entities outside of the University who are providing PHI to University researchers. In this case, the covered entity providing the PHI is responsible to ensure that HIPAA regulations are followed.
- Review and approval of all authorization documents used by University researchers when the authorization is combined with a consent form.
- Review and approval of waivers or alterations of authorization, including limited waivers of authorization, for access, use and/or disclosure of PHI for University research purposes.

29.1 HIPAA Authorization and Informed Consent

For Ohio University research that includes the creation or use of protected health information, in addition to following the informed consent procedures described in section

28.0, researchers generally must also obtain authorization for use of PHI from the human subjects whose PHI will be included in the study. The authorization document must include all elements defined in HIPAA. In certain cases, it may be acceptable for the authorization to be incorporated into the informed consent document. In such cases, all elements of the authorization must be included in the consent document.

29.2 Procedure for Signing an Authorization

Adults: A competent individual, 18 years of age or older, should always sign the authorization to use or disclose PHI. Competency refers to the general ability to understand the concept of release of medical information. If the patient is not conscious, coherent or not competent for whatever reason, a legally recognized proxy, such as a legal guardian, must sign the Authorization.

Minors: Any parent or legal guardian may sign an authorization for a minor child for which they have legal custody. Note that HIPAA does not require that an assent document specifically for research participation include any version of a HIPAA authorization.

Researchers who elect to obtain an electronic signature on the HIPAA authorization must obtain a letter of support that specifically endorses the electronic signature.

The individual must be provided with a copy of the signed Authorization.

29.3 HIPAA Waiver of Authorization:

In some circumstances, authorizations for research use of PHI may be waived by the IRB, provided the following criteria are satisfied and documented (generally in addition to satisfaction of waiver of informed consent requirements pursuant to 45 CFR 46.116 since many of the elements overlap):

The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on the presence of at least the following elements:

- An adequate plan to protect the identifiers from improper use and disclosure;
- An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
- Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by this Policy.
- The research could not practicably be conducted without the waiver; and
- The research could not practicably be conducted without access to and use of the PHI.

A request for Waiver of Authorization must be completed by the researcher and submitted to the IRB for prior review and approval. The IRB shall maintain documentation of the request and its approval. This request may be combined with a waiver of informed consent for research.

Uses or Disclosures of PHI made pursuant to a Waiver are subject to the Minimum

Necessary rules.

29.4 Limited Waiver of Authorization solely for the purpose of prescreening, contacting and/or recruiting potential research participants

In addition to the scenarios that would support a waiver of authorization for all study activities, there is the potential need to grant a Limited Waiver of Authorization solely for the purpose of prescreening, contacting and/or recruiting potential research participants. Since a researcher cannot practicably obtain a potential research participant's authorization for review of PHI in advance of contacting the potential participant, the IRB may issue a limited waiver of authorization permitting specified access and use of PHI solely for prescreening and recruitment contact pursuant to an approved protocol. An example of a scenario in which a limited waiver may be appropriate is if a researcher needs to review health care records to make recruitment contacts.

The IRB approval of a limited waiver of authorization will be in accord with the criteria for a waiver of authorization as applied to the prescreening, contact and recruitment procedures described in the protocol and IRB application.

Physicians and other health care professionals who have a direct treatment relationship with an individual may review that individual's PHI for eligibility with respect to a research protocol and may initiate a discussion with the individual about potential participation as a research subject in a protocol relevant to the treatment relationship. This scenario does not require an Authorization or a Waiver of Authorization.

References:

45 CFR 46.164

30.0 Special Topics: Research design and context

Some of the types of research described below may be eligible for exemption, but the IRB should be cognizant of the challenges and issues inherent in these types of research and should remember that all human subject protection guidelines apply to such research.

30.1 Research in educational settings

Research conducted in established or commonly accepted educational settings that involves normal educational practices as well as research involving the use of educational tests, survey procedures, interview procedures, or the observation of public behavior is eligible for exemption from the Common Rule. However, such research sometimes raises special concerns. One example of such a concern is the "two-hat" problem in which a researcher is also an instructor with potential coercive power or undue influence over students who are also potential research subjects. Such a situation does not automatically disqualify a project from exemption, but the reviewer should be cognizant of the problems such an arrangement might create. Furthermore, even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected. When educational institutions become engaged in the actual conduct of research, they may be required to file an assurance in accordance with 45 CFR 46.103(a).

30.2 Trainees as investigators

The role of Primary Investigator implies ultimate administrative and fiscal responsibility subject to University review and oversight as well as sufficient expertise for the research study and, as such, should be filled by a faculty member or staff member unless approved in advance. Though a trainee or another person may have primary responsibility for the intellectual content and may perform the research activities within the project, and may garner primary credit for any publication resulting from the research, the PI has ultimate administrative and fiscal responsibility for the project, subject to University review and oversight.

- If a grant program explicitly requires that a trainee investigator be listed as PI, that exception may be made; however, the faculty supervisor remains responsible for appropriate supervision of study compliance with all research ethical and regulatory requirements, including those related to human subjects protection.

Trainee investigators are students, postdoctoral employees, or fellows who have a significant, even primary, research responsibility for a protocol submitted to the IRB. These trainee investigators may conduct the majority of the research for a given protocol, but do not have ultimate administrative and fiscal responsibility for the project.

The primary responsibility for protecting the rights and welfare of human subjects in research performed by trainees rests with the faculty member supervising the trainee investigator. This faculty member must be identified in materials submitted to the IRB for review of the project. Faculty who assign or supervise research conducted by trainees or staff have an obligation to consider carefully whether those individuals are qualified to safeguard adequately the rights and welfare of subjects.

30.3 Trainee or student projects involving human subjects research

30.3.1 Student or trainee honors projects, theses and dissertations

Student or trainee research projects in the form of directed or independent research, such as a thesis, dissertations and honors research projects, are generally research intended to contribute to generalizable knowledge. When they involve human subjects, these projects require IRB review, as with any human subject research.

30.3.2 Student or trainee human subjects projects (class projects)

Class human subject research projects (not for thesis or dissertation) are often designed primarily to educate students in research techniques or issues, without an expectation of contributing to generalizable knowledge. However, since the lines between educational goals and research are sometimes difficult to demarcate, and class projects may still (either directly or through data about them) involve living persons, class projects may expose individual subjects to the same risks as research intended for broader purposes. Furthermore, since a major goal of a class project should be to educate students in the process of human subject research, instructors should make every effort to make the research process as realistic as possible.

Generally, relevant student projects will fall into one of the categories described below. In keeping with University policy, the instructor serves as the PI on every student project, with the full administrative and fiscal responsibility that normally accompanies that status (see section 2.4, which is entitled Primary Investigator (PI)).

30.3.2.1 In cases where a student will be performing a study that meets the federal definition of human subjects research, the study should be reviewed by the IRB so individual factors can be described and reviewed, and an approval determination made.

30.3.2.2 In cases where a student will be conducting a project that does not meet the federal definition of research, the instructor assumes responsibility.

30.3.2.3 In cases where all or many students in a class will be conducting very similar projects, the instructor may submit a single IRB application that describes these projects as a set. The instructor should be identified as the PI for the entire set of projects, and will hold the same responsibility for each individual project as the PI of a more targeted research protocol. The IRB application should include a general description of the aims of the class project(s), the types of activities to be performed, any variance across student projects (e.g., different datasets, different types of interactions with subjects, etc.), and any other factors that would help the IRB understand the nature of the project(s).

30.3.3 Training of student researchers

Instructors should actively instruct the students in the application of ethical principles and regulations as they apply to the class project, including respect for persons as it translates into informed consent, courtesy, avoidance of unnecessary discomfort, protection of privacy, etc. At their discretion, instructors may require students to complete the web-based education modules for human subject protection (CITI modules).

30.4 Pilot studies

Pilot studies may represent complex research even though they may be conducted as preludes to more expansive studies. Therefore, pilot studies must be reviewed by the IRB.

30.5 Oral histories as a type of humanities or social science research

OHRP declared in September, 2003, that oral history interviews, in general, are not designed to contribute to generalizable knowledge and, therefore do not meet the definition of 'research' in 45 CFR 46. Ohio University accordingly, does not require IRB review of oral histories unless such activities fall under a project that does meet the definition of research.

30.6 Qualitative research

Qualitative studies, which may involve such methods as participant observation, case studies, unstructured interviews, focus groups and various other descriptive techniques, raise special issues for the IRB. Qualitative research investigators usually have a well-articulated plan for their research, often have one or more reasonably specific hypotheses to be tested, and can describe in general terms the techniques they intend to employ. However, they may undertake research projects with the full expectation that techniques will be developed in the course of research, used on the basis of opportunity, and modified as events and experiences suggest are necessary for the success of the project. As a result, qualitative research investigators may present a research protocol that does not fit the usual model contemplated by federal human subject regulations for research, if those regulations are narrowly interpreted.

Reviewing qualitative research projects requires flexibility on the part of the IRB and is facilitated by a willingness to waive some of the elements of informed consent and approve

methods of consent that are culturally appropriate. If the study protocol approved by the IRB is intended to encompass development of one or more research instruments, it may also be necessary to give relatively wide professional latitude to scientists in the application of approved methods so that an investigator does not need to come back to the IRB repeatedly for approval of changes that would be considered normal and routine under the circumstances. However, the IRB should make clear to the investigator that significant changes, including all changes that could increase risk for the human subjects (for example, the addition of a new topic in a survey), must be approved in advance by the IRB. Finally, the IRB may need to consider an informed consent process that is multi-layered and takes place over time as the research develops and the investigator is better able to articulate both areas of further interest and the methods being employed for studying them. Whatever flexibility the IRB decides is appropriate in the specific research context, that determination must include adequate protection for the welfare and rights of the human subjects in that specific context.

30.7 Survey research

The IRB should pay particular attention to the following issues in survey research:

- Possibilities of undue influence in administration of the survey;
- Possibility of deductive disclosure based on demographic information garnered from subjects (subject confidentiality and privacy must be protected);
- The setting of the survey and the issues raised by such a setting;
- The mode of obtaining consent, especially when a waiver or alteration of consent is requested. Surveys may often involve a waiver of written consent and attention should be paid to the oral presentation of required elements of consent (e.g., review of phone script for telephone surveys).

30.8 Investigational New Drug (IND) and Investigational Device Exemption (IDE) studies

An IND/IDE is an exemption from the law that otherwise requires that a drug or biologic or device must be approved before it can be transported across state lines. Generally, this exemption is required whenever a research study uses a drug, biologic or significant risk device that has not received FDA marketing approval. An IND may also be required for a drug that does have FDA marketing approval if the research study proposes a use of the drug that was not included in the existing FDA approval. IND and IDE research studies are subject to the same new and continuing review requirements as described in this document for human subjects research, but they also require FDA approval for the proposed research use.

Most IND and IDE studies at the University are research protocols developed and sponsored by the commercial entity that is developing a drug or device pursuant to FDA regulations and is itself responsible for obtaining the IND or IDE approvals and for fulfilling all other FDA requirements for such a study. It is possible to have IND or IDE studies for which the study protocol has been developed independently by a university investigator and for which that investigator is responsible for obtaining the IND or IDE and for fulfilling all FDA required filings and other documentation.

The IRB is not required to monitor the investigator's performance of required FDA

paperwork. However, in reviewing the study the IRB should be mindful that in this context, the IRB review should include determination of whether an IND or IDE is required, and may also require more intense IRB scrutiny of the protocol and related risks as well as more guidance to the investigator regarding the scientific design, subject safety parameters, informed consent process, and other human subjects protection factors.

For emergency use of an investigational product, see section 20.0, which is entitled Emergency use of a test article.

For non-emergency situations, prospective IRB approval is required. Single patient use allows a physician to obtain access to an investigational drug upon receiving approval from the IRB. This approval is granted for the treatment of a single patient. The treatment use may occur only after IRB approval is obtained.

FDA regulations define a “humanitarian use device” (“HUD”) as a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year. Because of the extremely limited market for such devices, they do not receive full FDA review and approval. For this reason FDA requires prospective IRB approval (except in exceptional emergency situations) for any use of the HUD with human research subjects or with patients. The investigator or health care provider is required to submit an application for IRB review of the proposed HUD use. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA in accordance with 21 CFR 814.100-126. FDA regulations do not require informed consent for patient care uses of an HUD; however, Ohio University policy is to apply the Common Rule principles regarding informed consent (a) to all research uses of an HUD and (b) to patient care uses of an HUD as deemed appropriate by the IRB in the specific context and as may additionally be required by the health care provider.

30.9 Research involving radiation

Studies involving the use of radiation, such as those requiring patients to be X-rayed, are not eligible for expedited review, even if all of the other procedures in the study have been deemed minimal risk.

In addition, projects in which subjects are exposed to ionizing radiation at an Ohio University facility must receive approval from the Radiation Safety Committee before final IRB approval can be granted.

30.10 Multi-center studies for which Ohio University is the coordinating center

“Engaged site” is a term that OHRP applies to sites that “engage” in research and therefore need to be covered by a Federalwide Assurance. For multi-center studies, all study sites are engaged sites.

When an Ohio University researcher serves as the primary investigator for an entire multi-center study, or when Ohio University is a sponsor of a multi-center study, or when Ohio University is the coordinating center for a multi-center study, the University PI is responsible for notifying the IRB and also the Office of Research and Sponsored Programs, when the project is externally funded.

For such multi-center studies, it is the responsibility of the investigators at each research

site to provide documentation to the Ohio University IRB that the study at that site is conducted in compliance with federal regulations (45 CFR 46) and HIPAA listed in the initial application, all applicable state and local regulations, and ethical principles governing research involving human subjects. Each coordinating site must be approved before the study can be conducted at that site. Similarly, the other centers must obtain renewal in order for the project to be renewed. For each research site, the research must be reviewed and approved by an IRB that is linked to the assurance at that site and local investigators. In many cases, investigators at an FWA institution will have a local IRB to which they are responsible; if no such affiliation exists, then the Ohio University IRB may serve as the IRB of record for that investigator. See section 3.3, which is entitled Agreements to provide IRB review of research conducted by unaffiliated investigators.

The Ohio University PI is responsible for developing a Data Safety Monitoring Plan, as required by the IRB, and for implementing a system for reporting and reviewing all adverse events (AEs). If the IRB deems formal oversight by an independent Data Safety Monitoring Board (DSMB) to be necessary, and there is no external DSMB provided, the IRB may require oversight by an Ohio University DSMB.

30.10.1 Disagreements among designated IRBs in multi-center research

Ohio University IRBs welcome the input of IRBs at different institutions; however, the Ohio University IRB is ultimately responsible for the welfare of subjects at the University, and must make decisions accordingly.

In research in which the Ohio University IRB has agreed to rely on another IRB for review of a given study, the Ohio University IRB has the authority to rescind this authorization at any time.

30.11 Research using existing data and materials

Each separate human subjects research study requires IRB review and approval of the specific proposed study, regardless of whether the data set or research materials have been previously compiled.

Research involving the use of data meeting any one of the conditions below is not considered human subjects research and does not need to be reviewed by the IRB:

- Data on decedents;
- Data that have been stripped of all identifiers that could link that data to living persons;
- Data with extant identifiers that Ohio University, its employees, research collaborators, and agents are contractually forbidden from accessing.

Under federal regulations, research utilizing only the types of data described above is not considered human subjects research and need not be reviewed by the IRB. Nevertheless, in certain cases, the IRB may be called upon to review projects utilizing such data. The Office of Research Compliance recommends that projects be submitted in the LEO IRB system where an official determination of “no IRB review is required” can be documented.

Research involving the use of data meeting one of the following conditions is eligible for IRB exemption from continuing review:

- if these sources are publicly available (45 CFR 46.104(d)(4))
- 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 (45 CFR 46.104(d)(4))

When existing data sets contain identifiable private information about living individuals and these sets are not publicly available, IRB review and approval is required before research can proceed. The IRB must determine whether the information can be used without obtaining additional informed consent. As such, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the conditions under which the data were obtained, including contracts, informed consent or a HIPAA authorization.

If this is not the case, the IRB should consider whether it is appropriate to waive the informed consent requirements in accordance with 45 CFR 46.116(f)(3). In many cases, a waiver of consent will be appropriate. In other cases, the IRB may determine that the research can only proceed if the investigator obtains data with codes and identifiers removed in such a way as to preclude the investigator or the source maintaining the data set from establishing subjects' identities. If the proposed data set includes protected health information (PHI) the IRB must determine whether the original HIPAA authorization will cover the use of the data, or whether the IRB can waive authorization.

Prospective studies using materials (data, documents, records, or specimens) that will be collected for some purpose unrelated to the research may qualify for exemption. The IRB may use expedited procedures to review research that proposes to use materials (data, documents, records, or specimens) that will be collected in the future for non-research purposes.

The IRB review should include review of the terms and conditions under which the data or materials were originally obtained and released to the investigator. The purpose of this review is to make sure that the proposed new use is not incongruent with the original purpose and permissions or approvals. See section 29, which is entitled HIPAA and IRB Review.

30.11.1 Creation of tissue banks

IRB review of a research proposal using human specimens for research purposes is required to determine whether the proposed research use constitutes human subjects research or qualifies for an exemption. If there are any questions regarding potential biosafety issues and related regulations, the investigator should contact the Department of Environment, Health and Safety for guidance.

If the IRB determines that the proposed human specimen use constitutes a human subjects research project, and if the research project will create a human specimen collection that will not be destroyed upon completion of the immediate research study, then the collection must be presumed to constitute a human specimen repository maintained for possible future research projects. The IRB review of the proposal for research that will create the human specimen repository must include review of the following components: (a) collection of the human specimens (creation of the human specimen repository); (b) maintenance and management of the human specimen repository; (c) access to human

specimen material in the repository for use in specific research studies; and (d) destruction or disposal of the specimens, as detailed below.

(a) The collection phase of the project involves issues familiar to IRBs in individual research studies that do not create repositories, although human specimen collection involves special concerns. For example, depending on the sources and timing in obtaining human specimens, there may be sensitive recruitment procedure issues. The protocol should state whether the tissues will be screened for HIV, hepatitis or other diseases, and if so, to whom that information will be reported and what guidance will be provided to the human subject. Particular attention must be paid to informed consent for collection of human specimens, to provide that in addition to all of the usual requirements for informed consent, it informs the human subjects explicitly about the use of the specimens and any related personal information. See section 28.14, which is entitled Consent for use of stored samples and genetic testing.

(b) With respect to maintenance and management of the repository, the protocol should state clearly what institution will be responsible for the specimen repository. The IRB should receive the investigator's assurance that there has been adequate planning for the institutional resources required to perform the operations described for the proposed lifespan of the repository including any promised privacy protections, an adequate contingency plan for any institutional transfers of custody of the repository as well as the plan for destruction of the specimens. See 28.14, which is entitled Consent for use of stored samples and genetic testing.

(c) The section of the protocol addressing transfers from the specimen repository to investigators for use in specific research studies must also be reviewed. This section should note whether actual specimens will be shared with investigators or only data obtained from the specimens. Furthermore, it should clarify whether or not the transfer/access protocol adequately provides for the security and privacy protections and any restrictions on uses that were promised in agreements for establishing the repository. The relevant agreements may include one or more of the following: informed consent, waiver of informed consent, authorization or waiver of authorization, and/or any contracts with sponsors or agencies for creation or management of the specimen repository.

IRB approval of access/transfer protocols should include review of an application form for requesting samples and/or data from the repository, an application procedure that includes documentation of required IRB approvals as well as screening out potential recipients who do not provide adequate assurance of compliance with specimen transfer agreement, and a transfer agreement executed by the University.

If the access/transfer to material in the repository includes protected health information, HIPAA regulations apply. For example, for a "limited data set" pursuant to HIPAA, a data use agreement must include terms specified in HIPAA for such agreements. See section 29.0, which is entitled HIPAA and IRB Review.

(d) Investigators should make appropriate provisions for the disposal or destruction of specimens. These provisions should include procedures for maintaining the confidentiality of donors as well as for adhering to any guidelines related to the disposal of hazardous waste material.

Useful sources of information on human specimen repositories can be found at the

following sites:

- National Cancer Institute: “Organizational and Operational Aspects of Specimen Resources”
https://cdp.cancer.gov/resources/human_specimen/organizational_operational_aspects.htm
- International Society for Biological and Environmental Repositories (ISBER)
<http://www.isber.org/>

30.11.2 Data registries and databases (data bank)

If the research project under review is specifically intended to create a database that will contain individually identifiable data and will serve as an ongoing data resource for other researchers and other research projects, the IRB review of the proposal for creating the database should include all four of the database activities noted as (a), (b), (c) and (d) below. The level of detail should be appropriate to the size, complexity, sensitivity and anticipated pattern of use of the database. “Registry” is a term often applied to a large database of defined data elements that is designed to be updated and to support the ongoing exchange and use of data. Registries are sometimes created by a public authority (e.g., Central Cancer Registries). Regardless of whether the database is technically a registry, if it is created to serve as a data resource (herein referred to as a “data bank”), it must be consciously and appropriately managed. Useful guidance and links to helpful information on managing databases and data registries can be found at the NIH Data Sharing Policy and Implementation Guidance site at http://grants.nih.gov/grants/policy/data_sharing/.

The different activities in creating a data bank for future use are:

- (a) collection and use of the data for the immediate project;
- (b) maintenance and management of the data bank;
- (c) access to data in the data bank for use in future research studies;
- (d) disposal or return of the data.

(a) The collection phase of the project involves the issues familiar to IRBs in individual research studies; however, particular attention must be paid to the informed consent process to provide that in addition to all of the usual requirements for informed consent, human subjects are explicitly informed about the intended ongoing use of their information in the data bank.

(b) With respect to maintenance and management of the data bank, the IRB should receive the investigator’s assurance that there has been adequate planning for the institutional resources required to perform the operations described for the proposed lifespan of the data bank, including any promised privacy protections, an adequate contingency plan for any institutional transfers of custody of the data bank, as well as the plan for destruction or return of the data.

(c) The section of the protocol addressing future disclosures from the data bank for other research studies must also be reviewed. The transfer/access protocol should provide adequately for the security and privacy protections and any restrictions on uses that were promised in agreements under which the data were originally obtained. These relevant

agreements may include one or more of the following: informed consent, waiver of informed consent, authorization or waiver of authorization, data use agreement and/or any contracts with sponsors or agencies for creation or management of the data bank.

The IRB approval of access/transfer protocols should include review of the process for disclosing data from the data bank, including an application form that documents required IRB approval, and also including an institutionally approved data use or data transfer agreement. If protected health information is involved, HIPAA regulations may apply. A data use agreement for a "limited data set" pursuant to HIPAA must include terms specified in HIPAA for such agreements. Even without HIPAA involvement, written agreements for data use or data transfer agreements generally include provisions addressing the following:

The data bank custodian will not release any identifiers to the investigator.

The recipient investigator will not attempt to recreate identifiers or to identify individuals or institutions who are the subject of the data or individuals from whom the data were obtained.

The recipient investigator will use the data only for the purposes and research specified.

The agreement may include additional conditions imposed by the IRB as a condition of approval for creation of the data bank.

The recipient investigator is required to comply with IRB approval of the project for which current data access is sought.

The agreement generally includes requirements for disposal or return of the data by the recipient investigator.

(d) The IRB approved protocol for creation of the data bank must also address the anticipated lifespan of the data bank and the procedure(s) to be followed when it is dismantled, including appropriate confidentiality and privacy protections in the disposal of data.

30.12 Review involving data from voice, video, digital or image recordings

If researchers wish to utilize data from voice, video, digital or image recordings, they must take a variety of special precautions. The researcher must obtain appropriate permissions from subjects who will not have their anonymity protected due to the very nature of the data being collected. The information or fact sheet and/or informed consent document must explain the intended use of the voice, video or image data, the provisions being taken for the storage of the data, as well as the means and timeline planned for the destruction of this data. Specifically, the consent form must describe where the voice, video, or image data will be stored, who will have access to it, and the month and year by which it will be destroyed. Because of these unique constraints, researchers must take great care in authoring protocols in which the use of voice, video and image data are planned.

Certain studies involve the collection of voice, video and image data for the purpose of creating an archive or registry that will preserve the data indefinitely. In such cases, researchers will not make provisions for the destruction of data, and they should take care to inform participants of the archival nature of the data gathering performed in such a study.

30.12.1 Photographs

Some researchers use a method of qualitative data collection in which participants take photographs of some aspect(s) of their lives, environment, community, etc. The photographs are then used as a basis for group discussions and to elicit important qualitative information about the photographers' attitudes, beliefs, etc. The degree of risk to subjects in such research depends, in part, on what is photographed. For example, this process may pose the risk of self-incrimination to subjects who photograph themselves taking part in certain activities.

From the perspective of the IRB, the "human subjects" in the research are the research participants who are taking the photographs and then presenting their interpretations in group or other data gathering sessions. If the photographers are minors, then written parental consent for their participation in the research is required, along with assent of the minor participant.

Although the individuals whose photos are taken are not the subjects of the research, there may be legal requirements for obtaining permission for using their photographs. If the photographers take photos of other people, then permission to use the photo should be obtained. If the person being photographed is a minor, then permission to take the photo must be obtained from the child's parent or guardian. Those being photographed must be informed about how their photo will be used, and whether they will have the opportunity to view the photo before making a final decision about its use. If the photographs will be publicly displayed, such as at a professional meeting or community gathering, or used in manuals or brochures or other publications, then written consent to take and display the photograph publicly is required. Researchers must have a method to link pictures with the signed permission forms.

30.13 Research involving deception or withholding of information

Some research designs may require the withholding of information from human subjects. Research involving deception or withholding of information must be reviewed by the IRB with common sense and sensitivity. The withholding of information by researchers is different from the practice of deception, in which researchers provide false or misleading information to subjects. Studies involving deception need to be carefully reviewed by the IRB to ensure that the deception is justified through an examination of the risks and benefits of that deception. Furthermore, the IRB should ensure that, when appropriate, the subjects will be debriefed. Before approving a study that involves deception, the IRB should determine that the subject population is suitable. The IRB should also determine that the deceit involved in the study would not alter subjects' assessment of risk if they were aware of the deception at the time they agreed to participate. In some cases, the IRB may require that participants provide consent following the debriefing.

30.13.1 Deception can only be permitted where the IRB documents that a waiver of the informed consent requirements is justified according to 45 CFR 46.116(f)(3). The IRB must document that the following criteria have been satisfied:

- 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;
- If the research involves using identifiable private information or identifiable

biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

30.14 Research involving potentially addictive substances

When research involving potentially addictive substances is proposed, the IRB must consider the subjects' capacity to provide ongoing informed consent if judgment is diminished by exposure to the substances. There may also be unusual potential for coercion in some circumstances, for example, if such research involves subjects that are institutionalized.

The IRB must also be sensitive to the ethical context of the research, in that there may be other ethical dilemmas associated with these studies if they involve the use of deception or include randomization. It is critical that the IRB focus on the considerations of risk and benefit of such research. For more information, see section 30.13, which is entitled Research involving deception or withholding of information.

In addition, research involving substances that may impair the judgment of subjects must include provisions for the safety of those subjects both within the research setting and if those subjects choose to withdraw from research while in an impaired state. For example, if a subject who is legally intoxicated should choose to withdraw from a study, he or she cannot be permitted to drive from the research setting.

Potential human subjects with a history of addiction or with direct access to the class of substances in their work environment should be excluded from studies using potentially addictive substances, unless the IRB makes a determination that there is a compelling reason for their inclusion and the study includes all appropriate safeguards to reduce the risk for these subjects.

30.15 Genetic information in research

Research including genetic information about individuals is highly sensitive and requires that investigators take great care in handling this information. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained. Additionally, the consent form should include explicit descriptions of the type and scope of genetic information that will be collected and used in the research project as well as whether, when and how subjects will be informed of the results of genetic analysis conducted in the research and/or study conclusions, including outcomes not currently contemplated that may have implications for an individual (e.g., if a researcher discovers a gene linked to an incurable disease). Inevitably, such research decisions have implications for the confidentiality of identifiers linking subjects to their genetic data.

See also section 29.0, which is entitled HIPAA and IRB Review and section 32.8, which is entitled Third party research subjects. See also section 19 of the Office of Research Compliance Policies and Procedures book, which is entitled, "Guidance document on genetic testing and reporting of incidental findings."

30.16 Gene manipulation in human subjects research

All research involving gene transfer into human subjects or any form of recombinant DNA research must be reviewed by the University's Institutional Biosafety Committee. All recombinant DNA research must be reviewed and approved by the NIH's Recombinant DNA Advisory Committee (RAC). NIH guidelines on recombinant DNA and gene transfer research are available online at: https://osp.od.nih.gov/wp-content/uploads/2016/05/NIH_Guidelines.pdf

30.17 Human embryonic stem cell research

Federal regulation of human embryonic stem cell research is both complex and evolving. The IRB should contact the Office of the Vice President for Research/Creative Activity for assistance in arranging appropriate review of any research studies using human embryonic stem cells.

30.18 Human fetal tissue transplantation research

It is unlawful for any person to knowingly acquire, receive or transfer any human fetal tissue for valuable consideration. It is unlawful for any person to solicit or knowingly acquire, receive or accept a donation of human fetal tissue for transplantation if the tissue is obtained pursuant to an induced abortion and the donation is made pursuant to a promise that it will be transplanted to any specified individual, to a relative of the donating individual, or in valuable consideration for the costs associated with the abortion. Additionally, all other ethical and regulatory requirements for the welfare and protection of human research subjects apply to both the donors and the recipients of human tissue used in transplantation research.

Human fetal tissue may be used only if it has been obtained in accord with the following requirements: (1) the woman providing the tissue must declare in a signed written statement that she is donating the tissue without any restrictions regarding the identity of the transplant recipients and without being informed of the identity of the recipients; (2) the attending physician must declare in a signed written statement that the tissue was donated by the woman and with full disclosure with regard to the physician's interest in the research and any known medical or privacy risks associated with the research. If the tissue is obtained pursuant to an induced abortion, the attending physician must also declare in her or his signed written statement that the consent of the women for the abortion was obtained prior to requesting or obtaining consent for the donation of the tissue, no alteration of the timing, method or procedures used to terminate the pregnancy was made solely for the purpose of obtaining the tissue; and the abortion was performed in accordance with applicable state law; and (3) the PI for the research must declare in a signed written statement that: the tissue is human fetal tissue; the tissue may have been obtained pursuant to a spontaneous or induced abortion or stillbirth; the tissue was donated for research; the investigator had provided this information to other individuals involved in the research and received written acknowledgement of the receipt of this information; and the investigator has had no part in decisions to terminate the pregnancy.

REFERENCE: OHRP Guidance on "Fetal Tissue Transplantation" dated February 7, 2003.

Also see section 33.0, which is entitled Research involving pregnant women, human

fetuses and neonates.

30.19 Family history research

Family research typically involves obtaining information from one family member (called a proband) about other family members (third parties). For a detailed description of family history research, see section 32.8, which is entitled Third party research subjects.

30.19.1 Recruitment of family members via family history research

In some cases, researchers may learn about potential subjects through family history research and wish to enroll a third party in a study. In such situations, the researcher must exercise extreme care in approaching a third party via a proband.

Under most circumstances researchers should ask the proband to discuss participation in the research study with family member(s) before the researcher approaches those family members directly. Additionally, researchers should obtain consent directly from the family member(s) and not via the proband.

30.20 Internet research

The vast amount of social and behavioral information potentially available on the Internet has made it an important tool for researchers wishing to study the dynamics of human interactions and their consequences in this virtual medium. Researchers can potentially collect data from widely dispersed populations at relatively low cost and in less time than similar efforts in the physical world. However, the problem of subject identification and verification can severely limit this potential. For example, researchers could unknowingly involve protected populations or decisionally impaired subjects in the research study. There are also online data integrity issues.

Internet research protocols may involve research on the topic of the internet, research collecting data over the internet, observations of human behaviors on the internet, or some combination of these aspects. In evaluating studies utilizing the internet as a research tool, the IRB should ensure that investigators have a plan for:

- Obtaining and verifying informed consent if required;
- Maintaining the promised degree of privacy of subjects and confidentiality of information through the use of appropriate security measures; and
- Appropriate online data collection method and data validation checks.

For more information, see section 23 of the Office of Research Compliance Policy and Procedures book, which is entitled, "Office of Research Compliance (ORC) Guideline on Internet Research with Human Subjects."

30.21 Self-experimentation

Generally, researchers should not enroll themselves as subjects in a study that they are supervising. Such a practice presents obvious conflict of interest issues and a variety of other ethical and practical issues.

References:

Ethical And Legal Aspects of Human Subjects Research on the Internet, A report on an AAAS

Workshop, November 1999.

“Psychological Research Online: Opportunities and Challenges” dated 9/30/03 by Robert Kraut, Judith Olson, Mahzarin Banaji, Amy Bruckman, Jeffrey Cohen, Mick Couper.

31.0 Special Topics: International Research

IRB review of research studies that involve human subjects in other countries must include appropriate expertise for evaluation of the study in the context of the specific international setting(s) and study population(s).

In addition to the usual requirements for human subjects research, some issues particularly vital for IRB review for protection of human subjects in international populations are noted below. The questions listed below should not be understood as either prescriptive or exhaustive, but as guidance in assessing international research protocols.

31.1 Human subjects protection administration issues

- Training in ethical conduct of research must be carried out and documented (e.g., some large field studies have hundreds of field workers conducting interviews in 8 provinces of China, all speaking different languages). For more information on this issue, see section 24.12, which is entitled Required education and certification of investigators on human research ethics.
- The IRB must determine whether a local IRB or other local analogous review body exists to provide local context and guidance.
- The IRB must determine whether a Federalwide Assurance (FWA) is required for the local performance site.
- The IRB must determine whether data privacy protections are reasonable in the specific research setting.
- According to the NIH, when research takes place in a country with human subject protection laws similar to those of the United States, researchers should conform to local law. For example, research that collects personal data in or originating from European Union and European Economic Area states should conform to the data protection laws of the General Data Protection Regulation. Where local human subjects protections are less stringent, researchers should conform to United States law.

31.2 Risk

- The IRB must determine whether the study design anticipates and minimizes the political, social, economic and legal risks that are particular to prospective human subjects or their communities in the particular country and subculture.
- The IRB must determine whether the risks of adverse events are likely to be different in this population than in the same research performed elsewhere.
- The IRB must determine whether adequate resources are readily available for potential physical injuries or psychological discomfort sustained in the course of research.

31.3 Justice/Benefit

- The IRB must determine whether the study is responsive to the needs of the subject population and whether the benefits of the study will be available to this human subject population. In other words, researchers may not utilize a human subject population merely for their own convenience and without the prospect of benefit to that population. Consideration should be given to producing benefits for the population that will continue after the termination of the study.
- If the study includes an experimental health treatment intervention, the IRB must determine whether an established effective treatment exists and whether it is available to this subject population. Incorporation of a placebo arm for a study when an effective treatment exists is always a serious ethical issue, but scrutiny must be particularly intense when there are additional issues of potential vulnerability in the subject population. If it is determined that the research intervention is an effective treatment, the IRB must determine whether it will be available to the human subjects and the subject population following completion of the research study.

31.4 Understanding the protocol and consent process

- Group consent and individual consent: In some cultures, group consent by the family and/or the community may be an important adjunct or precursor to individual informed consent. It is important to keep in mind that although group consent may be appropriate and necessary, it is not a substitute for individual informed consent. The informed consent process should be designed to minimize the potential for coercion of the individual by the group.
- The IRB must determine how a minor is defined within the study and whether local laws defining who is an adult differ from United States laws. The IRB must also specify how researchers are to document “legal age” for giving consent (e.g., this comes up often with research on adolescents and reproductive health issues).
- In addition to the obvious necessity of conducting the informed consent process in the local language, the IRB review should address whether there are special dialects that need to be included. Translation of the informed consent documents should be performed by a qualified translator. Interpretation of the informed consent dialogue should not be performed by a family member or other individual who has a personal relationship with the participant. For more information, see section 28.12, which is entitled Obtaining consent from non-English speaking subjects.
- Literacy levels and diverse cultural experience may affect individuals in their ability to understand new concepts such as randomization, experiment versus treatment, use of placebos, etc. Thus, the IRB should judge whether the language and concept level is appropriate. In some cases, supplementary materials may be needed: diagrams, pictures, tools to communicate the concept of “chance,” etc.
- In cases where subjects do not read and write, or when signing documents may be a violation of local norms or customs, researchers must consider alternate methods of documenting consent. Thumbprints, marking an “x,” or an interviewer signing a statement attesting that oral consent was given by the subject are all possible modes of documenting consent in such cases.
- The question of compensation to the participant should also receive culturally-specific

review. The investigator should provide clear evidence that the incentive is not excessive in the local context (e.g., providing food in famine-stricken populations). Some comparison metric is needed when incentives are described (e.g., \$3 may seem small, but could be more than a day's wage; thus, an investigator should describe the incentive relative to a day's wage or cost of a meal, etc.).

References:

45 CFR 46.101(h)

45 CFR 46.107(a)

21 CFR 56.107(a)

21 CFR 312.120(c)(1)

21 CFR 814.15(a) and (b)

OHRP Guidance "Institutional Review Board (IRB) Knowledge of Local Context" 10/98

OHRP Guidance "International Research – An Introduction" 2/98

OHRP IRB Guidebook, Chapter VIII Section K

FDA 1998 Guidance for IRBs and Clinical Investigators "Non-Local IRB Review"

NBAC April 2001 Report and Recommendations of the National Bioethics Advisory on Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries

32.0 Special Topics: Research Subject Groups

FDA regulations and the Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable subjects. At the same time, there are also requirements that members of specific populations be permitted or encouraged to become human research subjects to ensure that specific populations are adequately represented in research and have access to potential benefits of such research. The IRB is required to ensure that it has adequate board representation or the input of appropriate external consultants to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

32.1 Elements to consider in research involving vulnerable subjects

- The methods of recruitment, selection and the inclusion/exclusion criteria should be considered by the IRB, as should informed consent, the confidentiality of data, and the willingness of the subjects to volunteer.
- Group characteristics such as economic, social, physical and environmental conditions should be considered to ensure that the research includes appropriate safeguards for the protection of vulnerable subjects.
- Applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations.
- Research studies involving potentially vulnerable subject groups should have adequate procedures in place for assessing and ensuring subjects' capacity, understanding and informed consent or assent. In some cases, researchers should be expected to enhance understanding for potentially vulnerable subjects.
- Whether or not additional safeguards are necessary to protect vulnerable subjects. Such safeguards could include IRB monitoring of the consent process or the creation of a waiting period between contact and enrollment to allow for family questions.

32.2 Pregnant women, human fetuses and neonates

For further information, see section 33.0, which is entitled Research involving pregnant women, human fetuses and neonates.

32.3 Prisoners

For information on the special considerations regarding research involving prisoners, see section 34.0, which is entitled Research involving prisoners.

32.4 Children

For further information on research involving children, see section 35.0, which is entitled Research involving children.

32.5 Decisionally impaired subjects

Decisionally impaired persons are those who have a diminished capacity for autonomous decision making due to a psychiatric, organic, developmental or other disorder that affects cognitive or emotional functions. Incompetence is a finding of a court of law and results in the appointment of a legally authorized representative for the individual judged incompetent by the court. While some decisionally impaired persons may have been declared legally incompetent and may have a court-appointed legally authorized representative, this is not necessarily the case for all decisionally impaired persons. See section 28.11, which is entitled Surrogate consent for subjects who are decisionally impaired.

Aside from issues of who may give legal permission for research participation of individuals who are decisionally impaired, there are many issues the IRB must consider in deciding whether to approve the possible participation of decisionally impaired persons in the research study.

The IRBs should take special care to consider issues such as (1) whether decisionally impaired persons may be suitable subjects for this project; (2) whether, if the study is of more than a minor increase over minimal risk, the study holds out the prospect of direct benefit to the individual in a risk-benefit ratio at least as favorable to the subject as that presented by available alternative approaches; (3) whether the informed consent process can be structured to be appropriate and effective within the limits of the individual's decisional capacity; (4) if surrogate consent will be used, whether assent will also be required; and (5) whether there are any circumstances under which a surrogate decision maker may enroll a decisional impaired individual in the study over the individual's objection or resistance.

For more information, see section 24 of the Office of Research Compliance Policy and Procedures book, which is entitled, "Office of Research Compliance (ORC) Guideline on Impaired Capacity and Consent."

32.6 Research involving other potentially vulnerable adult subjects

The IRB should be sensitive to the vulnerability of subjects resulting from unique socioeconomic factors. For example, an offer of financial compensation for participation in research may be interpreted as exploitive when directed toward impoverished subjects.

Additionally, cultural factors may affect the ability of some subjects to give informed consent. For example, if a local leader has urged (or required) participation in research, prospective subjects may not feel free to opt out of the study.

Finally, the IRB should consider any individuals who are in the middle of a traumatic or emergency situation (e.g., someone experiencing the catastrophic loss of a family member or a home) or otherwise under emotional duress to be potentially vulnerable.

32.7 Research involving decedents

Decedents are not human research subjects under the Common Rule; however, research on decedents may create living third-party research subjects. See Third party research subjects below, and also section 30.19, which is entitled Family history research. Additionally, HIPAA specifically addresses using the protected health information of decedents for research purposes, see section 29.0, which is entitled HIPAA and IRB Review.

32.8 Third party research subjects

Because the Common Rule defines a human subject as a living individual about whom an investigator obtains identifiable private information, the family members or others identified and described by the primary subject may be human subjects under the regulations if the investigators obtain identifiable private information about them. Third parties may become human subjects when researchers acquire private, factual information about those parties (as opposed to opinions of the primary subject about third parties).

In addition to considering the nature and volume of the information acquired by researchers about third parties, the IRB should:

- determine whether third party information is collected incidentally or deliberately;
- review the proposed uses of the third party information collected;
- consider the significance of the implications to be drawn from the third party information collected;
- evaluate the ability of the investigators to ensure that confidentiality is maintained for the third parties, which might include PIs recording the information in a manner that protects the identities of the third parties;
- consider the potential impact on the primary subject if a third party is classified as a human research subject.

Taking all of these considerations into account, IRBs must determine whether third parties are human subjects, and determine whether their informed consent is required or can be waived according to 45 CFR 46.116(f)(3).

32.9 Employees, students or trainees as research subjects

Employees, students and trainees of Ohio University may be vulnerable subjects, depending on the context of the specific research study proposed, because of the potential for perceived coercion in the student/trainee or employment relationship (regardless of the researcher's intentions). This is particularly the case if the research is being conducted by investigators in the employee's or student's department or in any situation in which (1)

recruitment materials are presented in a manner that could appear to the potential subjects to be closely related to their individual student/trainee or employment relationships, and (2) a power differential exists between the researcher and a prospective subject. If the proposed subjects are a part of the research team there may also be inherent conflicts of interest in their participation. Therefore, only in compelling circumstances will students or employees directly supervised by the researcher be allowed to participate in the research project. Compelling circumstances would be those in which (1) the participation of these individuals holds out reasonable likelihood of direct benefit to these subjects (e.g., treatment protocol for a condition experienced by the employee, student, etc.) and (2) the risks to and vulnerabilities of these employees, students or trainees have been eliminated or have been minimized.

When reviewing any protocol that may seek to recruit human subjects from among the research entity's employee, student or trainee populations, the IRB's review should include consideration of the potential vulnerabilities of such subject groups in the context of the specific proposed study.

Ohio University's Departments of Psychology and Marketing have a system in place whereby students participate in research for academic credit. Both of these departments have approved Standard Operating Procedures (SOPs) that outline the use of the respective student pools for human subjects research. The SOPs are available on the ORC webpage for reference by IRB members and researchers and are reviewed minimally every three years.

References:

- 21 CFR 50.23
- 21 CFR 56.104
- 21 CFR 312.7(a)
- 21 CFR 812.7(d)
- 21 CFR 814.100-126
- 45 CFR 46.101(b)
- 45 CFR 46.103(a)
- 45 CFR 46.103 (f)(2)
- 45 CFR 46.108(b)
- 45 CFR 46.109(e)
- 45 CFR 46.110
- 45 CFR 46.111(b)
- 45 CFR 46.116
- 45 CFR 46.117(a)
- 45 CFR 46.117(b)(2)
- 45 CFR 46.117(c)
- 45 CFR 46.203-7
- 45 CFR 46.301-6
- 45 CFR 46.401-8

Sept. 22, 2003 letter from OHRP to Linda Shopes, Pennsylvania Historical and Museum Commission and Donald A. Ritchie, Senate Historical Office

33.0 Research involving pregnant women, human fetuses and neonates

In addition to the general requirements for review of research by the IRB, prior research with animal subjects, and, if feasible, research with nonpregnant persons should form the basis of the risk/benefit assessment for fetal research. The proposed research should seek information not obtainable in any other way. If abortion is involved, the investigators may have no part in either the decision to abort or decisions about the timing or the method to be used; no change in the abortion procedure that would present more than minimal risk to the fetus or its mother can be introduced for research purposes. No monetary or other inducements (e.g., free care) may be offered to a woman to induce her to terminate her pregnancy for research purposes.

Pregnant women may be involved in several categories of research. IRB duties differ in each category, but the primary objectives are assessing: (1) whether the research holds out the prospect of direct benefit for the mother's health or for the fetus; and (2) the risks to the woman and to the fetus or infant.

33.1 Conditions required for pregnant women or fetuses to be involved in research

33.1.1 Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses [45 CFR 46.204(a)].

33.1.2 The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means [45 CFR 46.204(b)].

33.1.3 Any risk is the least possible for achieving the objectives of the research [45 CFR 46.204(c)].

33.1.4 If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions in section 28.0, which is entitled Informed Consent [45 CFR 46.204(d)].

33.1.5 If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions in section 28.0, which is entitled Informed Consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest [45 CFR 46.204(e)].

33.1.6 Each individual providing consent under 33.1.4 or 33.1.5 is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate [45 CFR 46.204(f)].

33.1.7 For children as defined in 45 CFR 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions in 35.0: Research involving children [45 CFR 46.204(g)].

33.1.8 No inducements, monetary or otherwise, will be offered to terminate a pregnancy [45

CFR 46.204(h)].

33.1.9 Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy [45 CFR 46.204(i)].

33.1.10 Individuals engaged in the research will have no part in determining the viability of a neonate [45 CFR 46.204(j)].

33.2 Conditions required for neonates of uncertain viability and nonviable neonates to be involved in research

33.2.1 Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates [45 CFR 46.205(a)(1)].

33.2.2 Each individual providing consent under sections 33.3 and 33.4, is fully informed regarding the reasonably foreseeable impact of the research on the neonate [45 CFR 46.205(a)(2)].

33.2.3 Individuals engaged in the research will have no part in determining the viability of a neonate [45 CFR 46.205(a)(3)].

33.2.4 The requirements of both sections 33.3 and 33.4 have been met as applicable [45 CFR 46.205(a)(4)].

33.3 Neonates of uncertain viability

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions are met:

33.3.1 The IRB determines that:

- i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, [45 CFR 46.205(b)(1)(i)] or
- ii. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; [45 CFR 46.205(b)(1)(ii)] and 33.3.2.

33.3.2 The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with section 28.0, which is entitled Informed Consent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest [45 CFR 46.205(b)(2)].

33.4 Nonviable neonates

After delivery, a nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

33.4.1 Vital functions of the neonate will not be artificially maintained; [45 CFR 46.205(c)(1)].

33.4.2 The research will not terminate the heartbeat or respiration of the neonate; [45 CFR 46.205(c)(2)].

33.4.3 There will be no added risk to the neonate resulting from the research; [45 CFR 46.205(c)(3)].

33.4.4 The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and [45 CFR 46.205(c)(4)].

33.4.5 The legally effective informed consent of both parents of the neonate is obtained in accord with section 28.0, which is entitled Informed Consent, except that the waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph [45 CFR 46.205(c)(5)].

33.5 Viable neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of 45 CFR 46.

References:

OHRP guidelines

45 CFR 46, subpart B (November 13, 2001 revision)

34.0 Research involving prisoners

34.1 Definition of research addressed in this section

A “prisoner” is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [45 CFR 46.303(c)].

The regulations covering research involving prisoners apply not only to research that targets prisoners or the prison setting, but also to subjects who become incarcerated following their enrollment or subjects for whom their incarceration is coincidental with their research involvement (e.g., a prisoner with cancer enrolled in a treatment oriented study that involves no other prisoners).

34.2 Issues to be addressed in reviewing research involving prisoners

When a proposal proposes to use prisoners as a study population, the IRB should ascertain whether that population was chosen simply out of convenience to the investigator. Because the population is relatively stable and the life is routine, prisons have in the past seemed ideal environments in many ways for the conduct of certain types of research. Some procedures that would inconvenience free subjects are not a burden to prisoners. Since prison pay scales are notably lower than those in the free world, the cost of using prisoners as subjects may be less than using those who are not prisoners. Unlike

the general civilian population, they are all in one place. However, the nature of incarceration may conflict with the ethical principle of autonomy.

The primary issue surrounding the participation of prisoners in research is whether prisoners have a real choice regarding their participation in research, or whether their situation prohibits the exercise of free choice. A secondary issue is whether confidentiality of participation and of data can be adequately maintained in the prison. These issues must be evaluated by both the Ohio University IRB as well as the Ohio Department of Rehabilitation and Corrections (ODRC) IRB (when the research is conducted in an ODRC facility).

The circumstances common in prisons create environments in which the offer to participate in research may create undue influence in favor of participation. The lack of control allowed prisoners and their desire to obtain the advantages offered to those who agree to participate may impair their ability to weigh fairly the risks and benefits involved in participation. An example of a situation potentially presenting undue influence may be one in which research participants are moved to special units where they are given additional medical care and where the living conditions may be better than those provided to the general prison population. Other rewards for participation, such as offering parole or a reduction in sentence, would likewise constitute an undue inducement. Even the opportunity to leave the prison cell and interact with people from outside the prison may act as an undue inducement to participate in research.

Another question is whether prisoner-subjects can ethically be paid for participation, and if so, how much. Where prisoners must earn money to purchase the means by which to maintain their health and personal hygiene, and one way to earn that money is by participating in research, the potential for undue influence also exists. In nonprison settings, paying subjects to participate in research is considered ethically acceptable, so long as it is commensurate with the inconvenience involved and/or expenses incurred, i.e., parking, transportation, childcare, etc. Paying prisoners the same amount that would be paid to nonprisoners may, however, be seen as unduly influential in a setting where inmates can earn only a small fraction of that amount for any other "work" activity. On the other hand, paying prisoners a fraction of what would be paid to nonprisoners can be seen as exploitive.

In addition to problems of undue inducement, the involvement of prisoners in research raises questions of burden and benefit. Prisoners should neither bear an unfair share of the burdens of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible.

Minimal risk, as defined for studies involving prisoners, is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. In assessing risk to prisoners, the IRB should ensure that the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers [45 CFR 46.303(d)].

Confidentiality is extremely difficult to maintain in a prison environment. In prisons, people do not move about freely; the movements of prisoners are carefully tracked. When inmates are moved around (e.g., to go to a research appointment), everyone will know

about it. Prison records, including health care records, are accessible to persons who in other settings would not have access to such personal information, thus compromising the security of confidential information.

Generally, research involving prisoners does not qualify for expedited review; however, in the event that such a research study does qualify for expedited review, a prisoner representative should be one of the designated reviewers.

34.3 Required findings

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

- (1) the research under review represents one of the categories of research permissible under 45 CFR 46.305(a)(2);
- (2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- (3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
- (4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the primary investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- (5) the information is presented in language that is understandable to the subject population;
- (6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- (7) where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

34.4 Permitted research involving prisoners

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

- (1) the institution engaged in the research must certify to the Secretary (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305; and
- (2) the Secretary (through OHRP) must determine that the proposed research falls within

the categories of research permissible under 45 CFR 46.306(a)(2). The categories of permissible research are the following:

(i) study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(Note that the definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk for other research, contained in 45 CFR 46, subpart A, 45 CFR 46.102(j))

(ii) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

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

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

34.5 Certification of prisoner research

Institutions that conduct HHS-supported research involving prisoners as human subjects must take several steps to certify that the research is permissible according to federal regulations.

It is sufficient to send a brief certification letter to OHRP that simply includes the certification statement required in 45 CFR 46.305(a), and a statement indicating that the IRB chose one of the four permissible categories of research in 45 CFR 46.306(a)(2). However, inclusion of the following recommended information may greatly expedite the prisoner certification process:

- In addition to the prisoner certification, researchers should submit the protocol application (which includes the protocol and any IRB submission materials, including consent forms) and the grant application(s) (and any grant award updates).
- Prisoner research certification letter, including:
 - o OHRP Assurance Number
 - o IRB Number for Designated IRB
 - o Site(s) where research involving prisoners will be conducted
 - o If prisoner research site is engaged in research, provide OHRP Assurance Number

- o DHHS Grant Award Number
- o DHHS Funding Agency Name
- o Funding Agency Grants/Program Officer Name and Phone #
- o Title of DHHS Grant
- o Title of Protocol - if the same as the title of the grant, please indicate as such
- o Version Date of Consent Document to be used with “prisoners”
- o Date(s) of IRB Meeting(s) in which protocol was considered including a brief chronology of:
 1. Date of initial IRB review
 2. Date of Subpart C reviews
 3. Type of IRB review
 4. Whether or not this is a special IRB review for prisoner issues
- o Primary Investigator(s)
- o Reason for IRB review
 1. Non-prison study in which subject has become incarcerated and PI wishes to continue subject’s participation in the study
 2. Non-prison study with at-risk population
 3. Non-prison study, majority of study population are non-prisoners but PI seeks to enroll some prisoners
 4. Minimal risk DHHS conducted or supported epidemiologic research, majority of study population are non-prisoners but PI seeks to enroll some prisoners, and the sole purpose of the study is either to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease
 5. Initial Subpart C review of study designed to be conducted in a prison or using prisoners—PI seeks to enroll already incarcerated subjects
- It would be helpful (but not required) if the prisoner certification letter contained the following information:
 - o Justification for the use of prisoners in the study - if applicable, delineate the protocol to be conducted in the prison from the overall project described in the grant application
 - o Study objectives or study aims
 - o Brief summary of study procedures
 - o Customary treatment or services at the prison (or alternative to incarceration) research site(s) for the condition being studied
 - o Description of how risks specific to a prison (or alternative to incarceration) setting are minimized
 - o Whether the prison site(s) are “engaged in research” and whether they have obtained an assurance with OHRP

- o Whether a Certificate of Confidentiality was obtained by PI for the study
- o Description of the recruitment procedures in the specific prison (or alternative to incarceration) setting
- o Description of how the consent form was altered for use with a prison population or specific prisoner and whether subsequently incarcerated subject will be reconsented.

References:

45 CFR 46, subpart C [See Appendix B: 45 CFR 46]

OHRP “Guidance on the Involvement of Prisoners in Research” May 23, 2003

35.0 Research involving children

IRBs reviewing research involving children as subjects must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB should weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects. An IRB member or a consultant to the IRB with appropriate background and experience should be involved in the review of any protocol involving children.

Procedures that usually present no more than minimal risk to a healthy child include: urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The IRB must also consider the extent to which research procedures would be a burden regardless of whether the child is accustomed to the proposed procedures. The assessment of risk and burden should also be informed by an understanding of the anticipated physical health, emotional maturity and other internal and external factors of the proposed population of pediatric subjects.

35.1 Research in health care settings

With respect to pediatric research involving health care interventions or medical procedures, the assessment of the probability and magnitude of the risk, may be different in sick children and may vary depending on the diseases or conditions the subjects may have. For example, obtaining blood samples from a hemophiliac child may present more than minimal risk to the child. On the other hand, IRBs may consider that children suffering from chronic illnesses who are accustomed to invasive procedures may not incur significant additional risk by involvement in research procedures related to their ongoing treatment, in contrast to children who have not had such experiences.

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

intervention.

35.2 Research in school settings

With respect to non-health care related research involving children in an educational setting, studies should be carefully examined to determine both the level of risk and the potential benefit for the subjects. The risks involved in social science research are rarely physical; however, children may be susceptible to emotional and psychological risks as well as risks to their social standing. In addition to these considerations, the informed consent process for children within an educational setting is often quite complex. As part of its review, the IRB would generally expect to see evidence that researchers have obtained permission from the school administration and included a letter of support in their proposal. Letters of support should be signed and dated on letterhead from the entity providing it and specifically state what the agency is agreeing to. In addition, provisions should be made for obtaining the permission of parents of each participating child and the assent of the child subject.

35.3 Categories of research involving children that may be approved by IRBs

35.3.1 Research not involving greater than minimal risk [45 CFR 46.404].

35.3.2 Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject. Research in this category is approvable provided: (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach [45 CFR 46.405].

35.3.3 Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational settings; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition [45 CFR 46.406].

35.3.4 Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research that is not approvable under 45 CFR 46.404, 46.405, or 46.406 may be conducted or funded by DHHS provided that the IRB, and the Secretary, after consultation with a panel of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles [45 CFR 46.407].

In all cases, the IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians. See Section 28.9, which is entitled Assent by children.

For further information on research involving children, see Appendix B: 45 CFR 46.

References:
OHRP guidelines

APPENDIX A: THE BELMONT REPORT

Office of the Secretary Ethical Principles and Guidelines for the Protection of Human Subjects of Research
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Members of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

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Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes¹ intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic

ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular

individuals.² By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.³

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's

considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it

possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- 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. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where 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.

Comprehension. 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.

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 suitable to give some oral or written tests of comprehension.

Special provision 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 incompetent

(e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent 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.

Voluntariness. 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. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to

the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits. One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

¹ Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

² Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

³ Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

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APPENDIX B: 45 CFR 46

§46.101 To what does this policy apply?

(a) Except as detailed in §46.104, this policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States. Institutions that are engaged in research described in this paragraph and institutional review boards (IRBs) reviewing research that is subject to this policy must comply with this policy.

(b) [Reserved]

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy and this judgment shall be exercised consistent with the ethical principles of the Belmont Report.⁶²

⁶²The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.- Belmont Report. Washington, DC: U.S. Department of Health and Human Services. 1979.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Federal department or agency but not otherwise covered by this policy comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations that provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations that may otherwise be applicable and that provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy, provided the alternative procedures to be followed are consistent with the principles of the Belmont Report.⁶³ Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, or to the equivalent office within the appropriate Federal department or agency, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures. The waiver notice must include a

statement that identifies the conditions under which the waiver will be applied and a justification as to why the waiver is appropriate for the research, including how the decision is consistent with the principles of the Belmont Report.

(j) Federal guidance on the requirements of this policy shall be issued only after consultation, for the purpose of harmonization (to the extent appropriate), with other Federal departments and agencies that have adopted this policy, unless such consultation is not feasible.

(k) [Reserved]

(l) Compliance dates and transition provisions:

(1) *Pre-2018 Requirements.* For purposes of this section, the *pre-2018 Requirements* means this subpart as published in the 2016 edition of the Code of Federal Regulations.

(2) *2018 Requirements.* For purposes of this section, the *2018 Requirements* means the Federal Policy for the Protection of Human Subjects requirements contained in this subpart. The general compliance date for the 2018 Requirements is January 21, 2019. The compliance date for §46.114(b) (cooperative research) of the 2018 Requirements is January 20, 2020.

(3) *Research subject to pre-2018 requirements.* The pre-2018 Requirements shall apply to the following research, unless the research is transitioning to comply with the 2018 Requirements in accordance with paragraph (l)(4) of this section:

(i) Research initially approved by an IRB under the pre-2018 Requirements before January 21, 2019;

(ii) Research for which IRB review was waived pursuant to §46.101(i) of the pre-2018 Requirements before January 21, 2019; and

(iii) Research for which a determination was made that the research was exempt under §46.101(b) of the pre-2018 Requirements before January 21, 2019.

(4) *Transitioning research.* If, on or after July 19, 2018, an institution planning or engaged in research otherwise covered by paragraph (l)(3) of this section determines that such research instead will transition to comply with the 2018 Requirements, the institution or an IRB must document and date such determination.

(i) If the determination to transition is documented between July 19, 2018, and January 20, 2019, the research shall:

(A) Beginning on the date of such documentation through January 20, 2019, comply with the pre-2018 Requirements, except that the research shall comply with the following:

(1) Section 46.102(l) of the 2018 Requirements (definition of research) (instead of §46.102(d) of the pre-2018 Requirements);

(2) Section 46.103(d) of the 2018 Requirements (revised certification requirement that eliminates IRB review of application or proposal) (instead of §46.103(f) of the pre-2018 Requirements); and

(3) Section 46.109(f)(1)(i) and (iii) of the 2018 Requirements (exceptions to mandated continuing review) (instead of §46.103(b), as related to the requirement for continuing review, and in addition to §46.109, of the pre-2018 Requirements); and

(B) Beginning on January 21, 2019, comply with the 2018 Requirements.

(ii) If the determination to transition is documented on or after January 21, 2019, the research shall, beginning on the date of such documentation, comply with the 2018 Requirements.

(5) *Research subject to 2018 Requirements.* The 2018 Requirements shall apply to the following research:

- (i) Research initially approved by an IRB on or after January 21, 2019;
 - (ii) Research for which IRB review is waived pursuant to paragraph (i) of this section on or after January 21, 2019; and
 - (iii) Research for which a determination is made that the research is exempt on or after January 21, 2019.
- (m) *Severability*: Any provision of this part held to be invalid or unenforceable by its terms, or as applied to any person or circumstance, shall be construed so as to continue to give maximum effect to the provision permitted by law, unless such holding shall be one of utter invalidity or unenforceability, in which event the provision shall be severable from this part and shall not affect the remainder thereof or the application of the provision to other persons not similarly situated or to other dissimilar circumstances.

[82 FR 7259, 7273, Jan. 19, 2017, as amended at 83 FR 28518, June 19, 2018]

§46.102 Definitions for purposes of this policy.

- (a) *Certification* means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.
- (b) *Clinical trial* means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.
- (c) *Department or agency head* means the head of any Federal department or agency, for example, the Secretary of HHS, and any other officer or employee of any Federal department or agency to whom the authority provided by these regulations to the department or agency head has been delegated.
- (d) *Federal department or agency* refers to a federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (*e.g.*, the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).
- (e)(1) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:
 - (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
 - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
- (2) *Intervention* includes both physical procedures by which information or biospecimens are gathered (*e.g.*, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- (3) *Interaction* includes communication or interpersonal contact between investigator and subject.
- (4) *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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.*, a medical record).

(5) *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

(6) *An identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

(7) Federal departments or agencies implementing this policy shall:

(i) Upon consultation with appropriate experts (including experts in data matching and re-identification), reexamine the meaning of “identifiable private information,” as defined in paragraph (e)(5) of this section, and “identifiable biospecimen,” as defined in paragraph (e)(6) of this section. This reexamination shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. If appropriate and permitted by law, such Federal departments and agencies may alter the interpretation of these terms, including through the use of guidance.

(ii) Upon consultation with appropriate experts, assess whether there are analytic technologies or techniques that should be considered by investigators to generate “identifiable private information,” as defined in paragraph (e)(5) of this section, or an “identifiable biospecimen,” as defined in paragraph (e)(6) of this section. This assessment shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. Any such technologies or techniques will be included on a list of technologies or techniques that produce identifiable private information or identifiable biospecimens. This list will be published in the FEDERAL REGISTER after notice and an opportunity for public comment. The Secretary, HHS, shall maintain the list on a publicly accessible Web site.

(f) *Institution* means any public or private entity, or department or agency (including federal, state, and other agencies).

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

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

(k) *Public health authority* means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

(l) *Research* means a systematic investigation, including research development, testing, and evaluation,

designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

- (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.
- (m) *Written, or in writing*, for purposes of this part, refers to writing on a tangible medium (e.g., paper) or in an electronic format.

§46.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.

- (a) Each institution engaged in research that is covered by this policy, with the exception of research eligible for exemption under §46.104, and that is conducted or supported by a Federal department or agency, shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements of this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for Federal-wide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office. Federal departments and agencies will conduct or support research covered by this policy only if the institution has provided an assurance that it will comply with the requirements of this policy, as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB (if such certification is required by §46.103(d)).
- (b) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.
- (c) The department or agency head may limit the period during which any assurance shall remain effective or otherwise condition or restrict the assurance.

(d) Certification is required when the research is supported by a Federal department or agency and not otherwise waived under §46.101(i) or exempted under §46.104. For such research, institutions shall certify that each proposed research study covered by the assurance and this section has been reviewed and approved by the IRB. Such certification must be submitted as prescribed by the Federal department or agency component supporting the research. Under no condition shall research covered by this section be initiated prior to receipt of the certification that the research has been reviewed and approved by the IRB.

(e) For nonexempt research involving human subjects covered by this policy (or exempt research for which limited IRB review takes place pursuant to §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8)) that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol).

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§46.104 Exempt research.

(a) Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories in paragraph (d) of this section are exempt from the requirements of this policy, except that such activities must comply with the requirements of this section and as specified in each category.

(b) Use of the exemption categories for research subject to the requirements of subparts B, C, and D: Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) *Subpart B.* Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.

(2) *Subpart C.* The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

(3) *Subpart D.* The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

(c) [Reserved]

(d) Except as described in paragraph (a) of this section, the following categories of human subjects research are exempt from this policy:

(1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude,

achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

(3)(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501

or for “public health activities and purposes” as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*

(5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(ii) [Reserved]

(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.

(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv). The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

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§46.105-46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

(b) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(c) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(d) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(e) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§46.108 IRB functions and operations.

(a) In order to fulfill the requirements of this policy each IRB shall:

(1) Have access to meeting space and sufficient staff to support the IRB's review and recordkeeping duties;

(2) Prepare and maintain a current list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, for example, full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant;

(3) Establish and follow written procedures for:

(i) Conducting its initial and continuing review of research and for reporting its findings and actions to the

investigator and the institution;

(ii) Determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

(4) Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of

(i) Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(ii) Any suspension or termination of IRB approval.

(b) Except when an expedited review procedure is used (as described in §46.110), an IRB must review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

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§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy, including exempt research activities under §46.104 for which limited IRB review is a condition of exemption (under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8)).

(b) An IRB shall require that information given to subjects (or legally authorized representatives, when appropriate) as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, not less than once per year, except as described in §46.109(f).

(f)(1) Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §46.110;

- (ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);
- (iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - (A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
 - (B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.
- (2) [Reserved]
- (g) An IRB shall have authority to observe or have a third party observe the consent process and the research.

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§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

- (a) The Secretary of HHS has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the FEDERAL REGISTER for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.
- (b)(1) An IRB may use the expedited review procedure to review the following:
 - (i) Some or all of the research appearing on the list described in paragraph (a) of this section, unless the reviewer determines that the study involves more than minimal risk;
 - (ii) Minor changes in previously approved research during the period for which approval is authorized; or
 - (iii) Research for which limited IRB review is a condition of exemption under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).
- (2) Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).
- (c) Each IRB that uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals that have been approved under the procedure.
- (d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research.

- (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
 - (1) Risks to subjects are minimized:
 - (i) By using procedures that are consistent with sound research design and that do not unnecessarily

expose subjects to risk, and

(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116.

(5) Informed consent will be appropriately documented or appropriately waived in accordance with §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

(ii) [Reserved]

(8) For purposes of conducting the limited IRB review required by §46.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §46.116(a)(1)-(4), (a)(6), and (d);

(ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §46.117; and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and

welfare of these subjects.

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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§46.114 Cooperative research.

(a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.

(b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

(i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

(ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent forms, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

- (3) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in §46.109(f)(1).
 - (4) Copies of all correspondence between the IRB and the investigators.
 - (5) A list of IRB members in the same detail as described in §46.108(a)(2).
 - (6) Written procedures for the IRB in the same detail as described in §46.108(a)(3) and (4).
 - (7) Statements of significant new findings provided to subjects, as required by §46.116(c)(5).
 - (8) The rationale for an expedited reviewer's determination under §46.110(b)(1)(i) that research appearing on the expedited review list described in §46.110(a) is more than minimal risk.
 - (9) Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this policy, as described in §46.103(e).
- (b) The records required by this policy shall be retained for at least 3 years, and records relating to research that is conducted shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form, or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Federal department or agency at reasonable times and in a reasonable manner.

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§46.116 General requirements for informed consent.

- (a) *General.* General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials is described in paragraph (e) of this section. General waiver or alteration of informed consent is described in paragraph (f) of this section. Except as provided elsewhere in this policy:
- (1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.
 - (2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.
 - (3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.
 - (4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.
 - (5) Except for broad consent obtained in accordance with paragraph (d) of this section:
 - (i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why

one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

(b) *Basic elements of informed consent.* Except as provided in paragraph (d), (e), or (f) of this section, in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

(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 that 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 that 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, if any, 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 and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

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

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

(c) *Additional elements of informed consent.* Except as provided in paragraph (d), (e), or (f) of this section, one or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative'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 and procedures for orderly termination of participation by the subject;
- (5) A statement that significant new findings developed during the course of the research that 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) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- (8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- (9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (*i.e.*, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

(d) *Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.* Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted as an alternative to the informed consent requirements in paragraphs (b) and (c) of this section. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

- (1) The information required in paragraphs (b)(2), (b)(3), (b)(5), and (b)(8) and, when appropriate, (c)(7) and (9) of this section;
- (2) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
- (3) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
- (4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
- (5) Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific

research studies;

(6) Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

(7) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

(e) Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials—(1) Waiver. An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (e)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) Alteration. An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (e)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

(i) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(A) Public benefit or service programs;

(B) Procedures for obtaining benefits or services under those programs;

(C) Possible changes in or alternatives to those programs or procedures; or

(D) Possible changes in methods or levels of payment for benefits or services under those programs; and

(ii) The research could not practicably be carried out without the waiver or alteration.

(f) General waiver or alteration of consent—(1) Waiver. An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (f)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) Alteration. An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (f)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) *Requirements for waiver and alteration.* In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

- (i) The research involves no more than minimal risk to the subjects;
- (ii) The research could not practicably be carried out without the requested waiver or alteration;
- (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

(g) *Screening, recruiting, or determining eligibility.* An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

- (1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
- (2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

(h) *Posting of clinical trial consent form.* (1) For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

(2) If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (*e.g.*, confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

(3) The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

(i) *Preemption.* The informed consent requirements in this policy are not intended to preempt any applicable Federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed in order for informed consent to be legally effective.

(j) *Emergency medical care.* Nothing in this policy is intended to 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 law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).

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§46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of

a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

(b) Except as provided in paragraph (c) of this section, the informed consent form may be either of the following:

(1) A written informed consent form that meets the requirements of §46.116. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.

(2) A short form written informed consent form stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative, and that the key information required by §46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

(c)(1) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

(i) That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

(iii) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

(2) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

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§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to Federal departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. Except for research waived under §46.101(i) or exempted under §46.104, no human subjects

may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Federal department or agency component supporting the research.

§46.119 Research undertaken without the intention of involving human subjects.

Except for research waived under §46.101(i) or exempted under §46.104, in the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted by the institution to the Federal department or agency component supporting the research, and final approval given to the proposed change by the Federal department or agency component.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the Federal department or agency through such officers and employees of the Federal department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a Federal department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that Federal department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head of either the conducting or the supporting Federal department or agency may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

§46.201 To what do these regulations apply?

- (a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.
- (b) The exemptions at Sec. 46.101(b)(1) through (6) are applicable to this subpart.
- (c) The provisions of Sec. 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in Sec. 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.
- (d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions.

The definitions in Sec. 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

- (a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
- (b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.
- (c) Fetus means the product of conception from implantation until delivery.
- (d) Neonate means a newborn.
- (e) Nonviable neonate means a neonate after delivery that, although living, is not viable.
- (f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
- (g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
- (h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

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

- (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

- (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
- (c) Any risk is the least possible for achieving the objectives of the research;
- (d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
- (e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- (f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- (g) For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- (i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

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

- (1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- (2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- (3) Individuals engaged in the research will have no part in determining the viability of a neonate.
- (4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

- (1) The IRB determines that:
 - (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
 - (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- (1) Vital functions of the neonate will not be artificially maintained;
- (2) The research will not terminate the heartbeat or respiration of the neonate;
- (3) There will be no added risk to the neonate resulting from the research;
- (4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- (5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

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

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

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates. The Secretary will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 only if:

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

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

- (1) That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or

(2) The following:

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

Subpart C—Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

§46.301 Applicability.

- (a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.
- (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.
- (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

- (a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
- (b) "DHHS" means the Department of Health and Human Services.
- (c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- (d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

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

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

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

- (1) the research under review represents one of the categories of research permissible under §46.306(a)(2);
- (2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- (3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
- (4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the primary investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- (5) the information is presented in language which is understandable to the subject population;
- (6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- (7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

- (1) the institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and
- (2) in the judgment of the Secretary the proposed research involves solely the following:
 - (A) study of the possible causes, effects, and processes of incarceration,

and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(B) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

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

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

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D—Additional DHHS Protections for Children Involved as Subjects in Research

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such no substantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

§46.402 Definitions.

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

- (a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
- (b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- (c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.
- (d) "Parent" means a child's biological or adoptive parent.
- (e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

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

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

- (a) the risk is justified by the anticipated benefit to the subjects;
- (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

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

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- (a) the risk represents a minor increase over minimal risk;
- (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

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

DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (e.g.: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) the research will be conducted in accordance with sound ethical principles;

(iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The

choice of inappropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

(1) related to their status as wards; or

(2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

APPENDIX C: 21 CFR 50

Subpart A— General Provisions

Section 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., 21 CFR parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518 520, 706, and 801 of the Federal Food, Drug and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted. (45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981)

Section 50.3 Definitions.

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321-392)).

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(b) *Application* for research or marketing permit includes:

(1) A color additive petition, described in part 71. (2) A food additive petition, described in parts 171 and 571. (3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §§ 170.30 and 570.30. (4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in § 180.1. (5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials described in section 406 of the act. (6) An investigational new drug application, described in part 312 of this chapter. (7) A new drug application, described in part 314. (8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320. (9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330. (10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter. (11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending or repealing regulations for these drugs, described in § 314.300 of this chapter. (12) An application for a biological product license, described in part 601. (13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601. (14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809. (15) An Application for

an Investigational Device Exemption, described in part 812. (16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513. (17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514. (18) An application for premarket approval of a medical device, described in section 515. (19) A product development protocol for a medical device, described in section 515. (20) Data and information about an electronic product submitted as part of the procedures for establishing, amending or repealing a standard for these products, described in section 358 of the Public Health Service Act. (21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4. (22) Data and information about an electronic product submitted as part of the procedures for granting amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

(d) *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator) and the employees are considered to be investigators.

(f) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, for example, corporation or agency.

(g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article as a control. A subject may be either a healthy human or a patient.

(h) *Institution* means any public or private entity or Agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) *Institutional review board (IRB)* means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) *Test article* means any drug (including a 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 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

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

(l) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law

to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(m) *Family member* means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship. (45 FR 36390, May 30, 1980, as amended at 46 FR 8950 Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51497, Oct. 2, 1996; 62 FR 39440, July 23, 1997)

Subpart B - Informed Consent of Human Subjects

Sec. 50.20 General requirements for informed consent.

Except as provided in Secs. 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence. [46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

Sec. 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article. (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject. (3) Time is not sufficient to obtain consent from the subject's legal representative. (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d) (1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver

of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met. (i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND. (ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness. (iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug. (iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission. (v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by Sec. 56.115(a)(2) of this chapter. (vi) DOD has explained: (A) The context in which the investigational drug will be administered, for example, the setting or whether it will be self-administered or it will be administered by a health professional; (B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and (C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug. (vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient. (viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product. (ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section. (x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter. (xi) DOD will provide adequate follow-up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product. (xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence. (xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request. (xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use. (xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria. (xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent. (xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information. (xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by Sec. 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve: (i) The required information sheet; (ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written); (iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and (iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations. [46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999]

Sec. 50.24 Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

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

(2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

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

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

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

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

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with Sec. 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly

disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor. [61 FR 51528, Oct. 2, 1996]

Sec. 50.25 Elements of informed consent.

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(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 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, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research related injury to the subject.

(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) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

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

(2) 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 and 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.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to 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 law.

Sec. 50.27 Documentation of informed consent.

(a) Except as provided in Sec. 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative

at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in Sec. 56.109(c), the consent form may be either of the following:

- (1) A written consent document that embodies the elements of informed consent required by Sec. 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.
- (2) A short form written consent document stating that the elements of informed consent required by Sec. 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

APPENDIX D: 21 CFR 56

Subpart A—General Provisions

§ 56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations. (b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[46 FR 8975, Jan. 27, 1981, as amended at 64 FR 399, Jan. 5, 1999; 66 FR 20599, Apr. 24, 2001]

§ 56.102 Definitions.

As used in this part: (a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321–392)).

(b) *Application for research or marketing permit* includes: (1) A color additive petition, described in part 71. (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35. (3) A food additive petition, described in part 171. (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1. (5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act. (6) An investigational new drug application, described in part 312 of this chapter. (7) A new drug application, described in part 314. (8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320. (9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330. (10) An application for a biologics license, described in part 601 of this chapter. (11) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in part 601 of this chapter. (12) An *Application for an Investigational Device Exemption*, described in parts 812 and 813. (13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860. (14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861. (15) An application for premarket approval of a medical device for human use, described in section 515 of the act. (16) A product development protocol for a medical device for human use, described in section 515 of the act. (17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act. (18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4. (19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003. (21) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act. (22) Data and information submitted in a petition for a nutrient content claim, described in § 101.69 of this chapter, and for a health claim, described in § 101.70 of this chapter. (23) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in § 190.6 of this chapter.

(c) *Clinical investigation* means 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 Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous for purposes of this part.

(d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part.

(g) *Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act.

(h) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

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

(j) *Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, for example, it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) *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.

(m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements. [46 FR 8975, Jan. 27, 1981, as amended at 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 65 FR 52302, Aug. 29, 2000; 66 FR 20599, Apr. 24, 2001]

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations. [46 FR 8975, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981]

§ 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the 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. [46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991]

§ 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B— Organization and Personnel

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate

review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. [46 FR 8975, Jan 27, 1981, as amended at 56 FR 28028, June 18, 1991; 56 FR 29756, June 28, 1991]

Subpart C— IRB Functions and Operations

§ 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

(1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

(c) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting. [46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28028, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

§ 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or (2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under § 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.

(f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

(h) When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that is ongoing on April 30, 2001 are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date. [46 FR 8975, Jan. 27, 1981, as amended at 61 FR 51529, Oct. 2, 1996; 66 FR 20599, Apr. 24, 2001]

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the FEDERAL REGISTER.

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor

changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in § 56.108(c).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects. [46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991]

§ 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects. (c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter. [46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 66 FR 20599, Apr. 24, 2001]

§ 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§ 56.114 Cooperative research

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D— Records and Reports

§ 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects. (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. (3) Records of continuing review activities. (4) Copies of all correspondence between the IRB and the investigators. (5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. (6) Written procedures for the IRB as required by § 56.108 (a) and (b). (7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section. [46 FR 8975, Jan. 27, 1981, as amended at 56 FR 28029, June 18, 1991; 67 FR 9585, Mar. 4, 2002]

Subpart E— Administrative Actions for Noncompliance

§ 56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a re-inspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB; (2) Direct that no new subjects be added to ongoing studies subject to this part; (3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or (4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

§ 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and (2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the FEDERAL REGISTER.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in § 56.123.

§ 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§ 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

§ 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

APPENDIX E: OHRP INFORMED CONSENT CHECKLIST

Awaiting updated checklist from OHRP

APPENDIX F: CONSENT FORM TEMPLATE

Ohio University Adult Consent Form With Signature

Title of Research:

Researchers:

IRB number:

You are being asked by an Ohio University researcher to participate in research. For you to be able to decide whether you want to participate in this project, you should understand what the project is about, as well as the possible risks and benefits in order to make an informed decision. This process is known as informed consent. This form describes the purpose, procedures, possible benefits, and risks of the research project. It also explains how your personal information/biospecimens will be used and protected. Once you have read this form and your questions about the study are answered, you will be asked to sign it. This will allow your participation in this study. You should receive a copy of this document to take with you.

Summary of Study

[Provide a concise, focused summary of the research and include key information to assist a potential participant in understanding why one may or may not want to participate in the study. This section should be organized and presented in a way that facilitates comprehension.]

Explanation of Study

This study is being done because...

If you agree to participate, you will be asked to...

You should not participate in this study if... *[List exclusionary criteria, if applicable]*

Your participation in the study will last...

Risks and Discomforts

Risks or discomforts that you might experience are... **OR**

No risks or discomforts are anticipated.

Benefits

This study is important to science/society because...

Individually, you may benefit... **OR**

You may not benefit, personally by participating in this study.

Confidentiality and Records

Your study information will be kept confidential by...

Additionally, while every effort will be made to keep your study-related information confidential, there may be circumstances where this information must be shared with:

- * Federal agencies, for example the Office of Human Research Protections, whose responsibility is to protect human subjects in research;
- * Representatives of Ohio University (OU), including the Institutional Review Board, a committee that oversees the research at OU;
- * ***[Insert sponsors of the research, if any, who will have access to identifiable data and/or biospecimens]***

Compensation

As compensation for your time/effort, you will receive...

Please be aware that certain personal information, such as name, address and social security number, may be provided to the Ohio University Finance Office to document that you received payment for research participation. However, your study data will not be shared with Finance.

OR

No compensation will be provided. ***[Or remove the compensation section completely]***

Future Use Statement

Identifiers might be removed from data/samples collected, and after such removal, the data/samples may be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

OR

Data/samples collected as part of this research, even if identifiers are removed, will not be used for future research studies.

AND, where applicable:

Identifiable or de-identified biospecimens may be used for commercial profit. ***[Indicate whether or not the profit will be shared with the participant]***

Clinically relevant research results will be given to the subject. ***[Describe under what conditions this will happen]***

This research will or might include whole genome or exome sequencing of biospecimens.

Contact Information

If you have any questions regarding this study, please contact the investigator ***[insert investigator's name, email and phone number]*** or the advisor ***[insert advisor's name, email and phone number]***.

If you have any questions regarding your rights as a research participant, please contact Dr. Chris Hayhow, Director of Research Compliance, Ohio University, (740)593-0664 or hayhow@ohio.edu.

By signing below, you are agreeing that:

- you have read this consent form (or it has been read to you) and have been given the opportunity to ask questions and have them answered;
- you have been informed of potential risks and they have been explained to your satisfaction;
- you understand Ohio University has no funds set aside for any injuries you might receive as a result of participating in this study;
- you are 18 years of age or older;
- your participation in this research is completely voluntary;
- you may leave the study at any time; if you decide to stop participating in the study, there will be no penalty to you and you will not lose any benefits to which you are otherwise entitled.

Signature _____ Date _____

Printed Name _____

Version Date: *[insert mm/dd/yy]*

APPENDIX G: CONFIDENTIALITY STATEMENT

[The following agreement should be signed by all members and guests attending IRB meetings. Members may sign once and have their agreement kept on file.]

I acknowledge that confidential, proprietary and/or other sensitive information may be distributed or discussed at meetings of an Institutional Review Board (IRB) of Ohio University. Except to the extent disclosure may be required by law, I affirm that I will hold in strictest confidence all information I receive during the course and scope of my service to the IRB and/or attendance at IRB meetings.

(Signature)

(Printed name)

(Date)

(Role in IRB review, i.e. IRB member, researcher, guest, consultant)

APPENDIX H: Office of Research Compliance Organizational Chart

