University of Colorado Denver | Anschutz

Colorado Multiple Institutional Review Board (COMIRB)

Policies and Procedures for the Protection of Human Subjects

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UNIVERSITY OF COLORADO DENVER I

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD (COMIRB) I

POLICIES AND PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS I

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1 Mission

1.1 *Introduction*

The Colorado Multiple Institutional Review Board (COMIRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of:

- University of Colorado Denver
- Denver Health and Hospital Authority
- Rocky Mountain Veterans Affairs Medical Center (VA Eastern Colorado Health Care System)
- Children's Hospital Colorado
- University of Colorado Health

Mission Statement
To protect human research participants' rights and welfare and to facilitate ethical research

Goals

- Provide high-quality, timely, and consistent reviews of human research
- Provide exceptional customer service
- Provide effective consultation, training and guidance for researchers

In the review and conduct of research, actions by COMIRB will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (often referred to as the Belmont Report) and will be performed in accordance with the Department of Health and Human Services (HHS) policy, and regulations at 45 CFR 46 (also known as the "Common Rule"), and the Food and Drug Administration (FDA) policy, and regulations at 21 CFR 50 and 21 CFR 56. When following ICH-GCP (E6), Clinical Trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements. Additionally, to honor its commitment to the VA MEDICAL CENTER, COMIRB abides by the Department of Veterans Affairs policies for human research protection, including the regulations at 38 CFR 16, and the VHA Directive 1200.05. The actions of COMIRB will also conform to all other applicable federal, state, and local laws and regulations.

1.2 *Ethical Principles: The Belmont Report*

The Colorado Multiple Institutional Review Board (COMIRB) reviews protocols for research involving human subjects. The primary responsibility of the IRB is the protection of research subjects from undue risk and from deprivation of personal rights and dignity. This protection is best assured by consideration of three principles, which are the touchstones of ethical research:

(1) that voluntary participation by the subjects, indicated by free and informed consent, is assured;
(2) that an appropriate balance exists between the potential benefits of the research to the subject or to society and the risks assumed by the subject; and

(3) that there are fair procedures and outcomes in the selection of research subjects.

These principles are summarized as respect for persons, beneficence, and justice.

1.2.1 Respect for Persons: Voluntary Participation and Informed Consent

One of the most important elements in any research involving human research subjects is the assurance of voluntary informed consent. Any person who is to be a research subject, whether designed for their own direct benefit or for the advancement of scientific knowledge in general, must understand as completely as possible what is to be done and what the potential risks and benefits are. The person must give their consent freely, without pressure or inappropriate inducement. COMIRB strives to ensure voluntary informed consent of research subjects through careful review of the recruitment and consent process, and of the consent documents.

The informed consent concept is extended to those studies in which the subjects are not able to give personal consent for themselves. Here the consent document is addressed to those who have been designated responsible for the research subject's well-being (e.g. parents of children). COMIRB's concern is to verify that the consent process and document are likely to assist these persons to make an informed decision, which is in the best interest of the research subject. The capacity for truly informed and voluntary participation in research varies widely among study populations. At one extreme there may be ample understanding and manifest freedom from coercion; at the other, there may be degrees of understanding and freedom that affect the consent of potential subjects. The IRB must exercise special care when considering subjects whose ability to give free and informed consent may be compromised in any way.

1.2.2 Beneficence: The Risk-Benefit Ratio

COMIRB is charged with deciding, for any proposed activity which falls under its jurisdiction, whether: "The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept (those) risks" (Federal Register, May 30, 1974).

The assessment of the risk/benefit relation is a complex task. There are risks of injury or discomfort to the individual that can be physical, psychological and/or social. There can be potential benefits to the individual, to a group to which the individual belongs, and/or to society. When reviewing applications, COMIRB must carefully assess the types and degrees of both risks and benefits for a given subject population, as well as the investigator's communication of these risks and benefits in the consent process and form. While COMIRB is not charged with reviewing scientific design per se, it must sometimes do so in order to assess the risk/benefit ratio. If a study design does not seem adequate to attain the stated aim of the investigation, then no benefit can be anticipated from conducting the study, and there is no justification for placing any research subject at risk, however minimal. Thus the design of the study must be sound, and the nature and likelihood of all risks and benefits must be made clear in any application to COMIRB.

1.2.3 Justice: The Fair Selection of Subjects

Both the risks and the potential benefits of research should be spread fairly among potential individual research subjects and research subject groups. Study design and selection of subjects should avoid bias for or against a particular group.

1.2.4 Sharing Research Risks

The guiding principle in the ethical selection of research subject groups is that any risks of the research should fall upon the groups who might benefit from the research. If the results of a risky protocol might benefit the general population, it would be unethical to focus subject recruitment on vulnerable or disadvantaged groups (e.g. institutionalized people or prisoners; patients at free clinics primarily patronized by people unable to afford other medical care) simply because they are easily accessible or can be persuaded to participate. An undue share of research risks should not burden groups already burdened by other factors. Rather, attempts should be made to include a fair sampling of the populations who might benefit from the study.

When research involves persons whose autonomy is compromised, it is expected that the research bear some direct relationship to the conditions or circumstances of the research subject population. In addition, groups fully able to consider research risks and informed consent should be asked to face research risks before more vulnerable populations. Investigational drugs are usually tested in adults before they are tested in children. Certain investigational drugs and procedures may be tested in healthy volunteers before being tested in patients.

1.2.5 Sharing Research Benefits

In recent years, increasing attention has been paid to the rights of various groups to be included in research. As individuals and through advocacy groups, many patients have come to insist on having access to experimental treatments that may potentially provide the best medical care available. In addition, researchers, ethicists and public officials have recognized that because many clinical trials focus primarily on white middle-class subjects, the results of some trials were of questionable value for members of other groups. As a result, both the National Institutes of Health and the FDA now require that study design include as broad a range of research subjects as feasible and the data be analyzed to uncover responses that differ between groups. Where women of child-bearing potential and pregnant and nursing women previously were routinely excluded from new drug trials, it is required that whenever possible these women be asked to make their own choices after being fully informed of the risks of the research.

2 Definitions

2.1 *Human Subjects Research*

For the purposes of this policy “human subject research” is defined as an activity that meets the definition of “research” and involves “human subjects” as defined either by the Common Rule or by FDA regulations.

In this document, references to the “Common Rule” and 45 CFR 46 refer to both the 2018 Requirements and the Pre-2018 Requirements unless otherwise noted. The applicability of the 2018 Requirements or the Pre-2018 Requirements to particular research are addressed where necessary in subsequent sections.

2.1.1 Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this

definition may be funded or unfunded, or may be conducted as a component of another program not usually considered research. For example, demonstration and service programs may include evaluation components, which constitute research activities under this definition.

For the purposes of this policy, a “systematic investigation” is an activity that involves a methodological study plan (data are collected in an organized, consistent manner), which incorporates data collection (prospective and/or retrospective, quantitative and/or qualitative), and data analysis to answer a study question. As an example, COMIRB does not consider a case report of one or two patients to be a systematic investigation, whereas COMIRB does consider a case series of three or more patients to be systematic.

Investigations "designed to develop or contribute to generalizable knowledge" are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings. As examples preliminary data collected only for grant submissions (and not used in subsequent publications), would not be considered data that would contribute to generalizable knowledge. Instrument development that includes initial focus groups to refine the tool would not contribute to generalizable knowledge; however, focus groups to formally validate the tool would contribute to generalizable knowledge.

The following activities are not considered research under the Common Rule:

- 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.
- Public health surveillance activities conducted by a public health authority, 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 the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority.
- Including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products.
- Including 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).
- 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.
- Authorized operational activities (as determined by the relevant federal agency) in support of intelligence, homeland security, defense, or other national security missions.

Research as defined by FDA regulations 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 FDA under section 505(i) or 520(g) of the Federal Food, Drug,

and Cosmetic Act, or need not meet the requirements for prior submission to the FDA under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations [21 CFR 50.3 (c), 21 CFR 56.102(c)].

- *A* "Clinical investigation" using drugs means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. An "experiment" is any use of a drug except for the use of a marketed drug in the course of medical practice [21 CFR 3 12.3(b)]. Experiments using drugs that must meet the requirements for prior submission to the FDA under section 505(i) of the Federal Food, Drug, and Cosmetic Act are those which are not exempt from 21 CFR 312.
- Experiments using devices means any activity that evaluates the safety or effectiveness of a device [21 CFR 812.2(a)]. Experiments that must meet the requirements for prior submission to the FDA under section 520(g) of the Federal Food, Drug, and Cosmetic Act are those which are not exempt from 21 CFR 812.
- Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research [21 CFR 50.3(c), 21 CFR 56.102(c)].

Research under Department of Education regulations:
Research or experimental program or project means any program or project designed to explore or develop new or unproven teaching methods or techniques.

2.1.2 Human Subject as defined by the Common Rule

A living individual about whom an investigator (whether professional or student) conducting research:

Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

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Intervention includes both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

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.

An identifiable biospecimen is a biospecimen for which the identity of the subject is or may be readily ascertained by the investigator or associated with the biospecimen.

2.1.3 Human Subject as Defined by FDA Regulations

Any individual who is or becomes a subject in research; either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient with a disease. In the case of medical device research, a human subject/participant also means a human on whom or on whose specimen (even if unidentified) an investigational device is used.

2.1.4 Human Subject Research Involving the Department of Defense (DoD)

Human Subject Research involves the DoD when any of the following apply:

- The research is funded by a component of the DoD (e.g. Navy, Army, Air Force)
- The research involves cooperation, collaboration, or other type of agreement with a component of DoD
- The research uses property, facilities, or assets of a component of DoD
- The subject population will intentionally include personnel (military or civilian) from a component of DoD

Note: DoD policies and requirements do not apply when DoD personnel incidentally participate as subjects in research that is not supported by DoD, and DoD personnel are not an intended population of the research.

UC Denver I Anschutz Medical Campus has not signed an addendum with DoD and so all research involving DoD must also be submitted to a DoD IRB for review and approval before the research can begin. In accordance with DoDI 3216.02, a non-DoD institution engaged in non-exempt DoD-supported human subject research must rely on a Federal-Wide Assurance (FWA) or comparable federal assurance. The University maintains an FWA covering such research; investigators not covered by the University's assurance must be covered through an Individual Investigator Agreement with an assured institution. A federal assurance is not required when an institution's role is limited to exempt research or activities determined not to be human subject research.

For DoD-supported research reviewed by COMIRB, the sponsoring DoD component's Human Research Protection Official (HRPO) must review and approve the research before it may begin, in addition to COMIRB approval. For DoD-conducted research in which a DoD institution relies on COMIRB for IRB review, see Section 4.3.1.

For greater than minimal risk research involving DoD-personnel, when recruitment and consent occur in a group setting, the DoD IRB must appoint an ombudsperson. The ombudsperson must not have a conflict of interest with the research or be a part of the research team. The study team will be required to identify the ombudsperson to COMIRB when necessary and with appropriate documentation.

When following Department of Defense regulations, the IRBs determine that the disclosure includes that provisions for research-related injury follow the requirements of the DoD component.

In accordance with DoD Instruction 3216.02, Service members and all Reserve component and National Guard members in a federal duty status are considered to be adults. If a

Service member, Reserve component or National Guard member in federal duty status, student at a Service Academy, or trainee is under 18 years of age, the IRB/EC must carefully consider the participant recruitment process and the necessity of including such member as a human participant.

There are additional Department of Defense safeguards for research conducted with international populations. See section 18.6 below.

2.2 *COMIRB*

Colorado Multiple Institutional Review Board, the IRB for the University of Colorado Denver | Anschutz Medical Campus and its affiliate institutions.

2.3 *IRB*

Institutional Review Board established in accord with 21 CFR 56 and 45 CFR 46.

2.4 *IRB Approval*

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.

2.5 *Minimal Risk*

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.

When following DoD requirements, the definition of minimal risk in Part 219 of Title 32, CFR, does not include the inherent occupational risks that certain subjects face in their everyday life, such as those:

- Encountered by Service members, law enforcement, or first responders while on duty.
- Resulting from or associated with high-risk behaviors or pursuits.
- Experienced by individuals whose medical conditions involve frequent tests or constant pain.

2.6 *Certification*

The official notification by the institution to the supporting Department or Agency, 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.

3 Organizational Structure

3.1 *Authority*

COMIRB is empowered to act by the University of Colorado Denver | CU Anschutz Chancellors as described in the UCD Policy on Human Research Protections Program (HRPP) initially adopted February 2008.

COMIRB provides IRB review for human subjects research for UCD and CU Anschutz, in accordance with the UCD | CU Anschutz Human Research Protections Program, or conducted at the participating institutions under a Cooperative Agreement or Memorandum of Understanding between the UCD | CU Anschutz Chancellors and Chief Executive Officers, Presidents and Directors of the Participating Institutions.

The Institutional Official is appointed by authority designated by the Board of Regents to the Chancellors of the Anschutz and Denver campuses. The Associate Vice Chancellor for Regulatory Compliance is the Institutional Official and works closely with the VC for Research to coordinate the human research protection program for CU Denver I Anschutz Medical Campus.

Pursuant to federal regulations and the above-mentioned UCD policy and agreements, COMIRB is authorized to:

1. Approve, require modifications to secure approval, or disapprove human subject research.
2. Suspend or terminate research for continued and/or serious noncompliance with the Common Rule, FDA regulations, or its own findings, determinations, and requirements.
3. Suspend or terminate research that has been associated with unexpected serious harm to participants.
4. Observe and/or monitor research (including the consent process) to whatever extent it considers necessary to protect human subjects.

COMIRB ensures that appropriate safeguards exist to protect the rights and welfare of research subjects [45 CFR 46]. In fulfilling these responsibilities, the panel reviews all the research documents and activities that relate directly on the rights and welfare of the subjects of proposed research. The protocol, the consent/assent document(s), the investigator's brochure when applicable, tests, surveys, questionnaires and similar measures, and recruiting documents are examples of documents that each panel uses to conduct its review.

Before any human subject is involved in research in relationship to this institution, COMIRB will give proper consideration to:

1. the risks to the subjects;
2. the anticipated benefits to the subjects and others;
3. the importance of the knowledge that may reasonably be expected to result; and
4. the informed consent process to be employed.

COMIRB is registered with the DHHS Office of Human Research Protections under: ***IORG0000433***.

3.2 *Jurisdiction*

COMIRB has jurisdiction over all human subject research conducted under the authority of affiliate institutions unless delegated to a central IRB to be the IRB of Record for a specific protocol.. Research under the authority of the institutions includes research conducted at the institution, conducted by or under the direction of any employee or agent of the institution (including students) in connection with their institutional responsibilities, conducted by or under the direction of any employee or agent of the institution using any property or facility of the institution, or involving the use of the institution's non-public information to identify or contact human subjects.

All institutional and non-institutional performance sites for participating institutions, domestic or

foreign, will be obligated by this institution to conform to ethical principles which are at least equivalent to those cited above or as may be determined by the Department of Health and Human Services (DHHS) Secretary.

3.3 *COMIRB Panels*

COMIRB comprises of five IRB panels. Each IRB panel consists of nine primary members and their designated alternates.

COMIRB IRB Registration #s

Panel A: # IRB00000648 [Primarily adult subjects: biomedical and social/behavioral]

Panel B: # IRB00000650 [Adult and pediatric subjects: biomedical and social/behavioral]

Panel C: # IRB00000651 [Primarily pediatric subjects: biomedical and social/behavioral]

Panel D: # IRB00002760 [Primarily adult subjects: primarily oncology and cardiology]

Panel S: # IRB00006846 [Primarily adult subjects: social/behavioral]

The Institutional Official (IO), the Director of the IRB Office, and the Chairs of the IRBs review the activities and IRB rosters of COMIRB at least annually to make sure the institution has the appropriate number and composition of IRB panels. Usually this takes place at convened meetings of the COMIRB Compliance Board.

3.4 *Use of an External IRB*

UCD-Anschutz Medical Campus has developed relationships with a variety of external IRBs. The Associate Vice Chancellor for Regulatory Compliance (IO) is responsible for establishing the regulatory framework outlining the roles and responsibilities of UCD in collaboration with its affiliated hospitals when applicable. The External IRB coordinator will coordinate activities with the external IRB but UCD retains the right to determine that a specific protocol must be reviewed locally.

Generally, UCD retains responsibilities for ensuring that investigators and staff are appropriately trained, that research personnel's conflicts of interest are appropriately managed, and for privacy board review when an external IRB is utilized but the specific details are governed by the specific memorandum of understanding, reliance agreement, and institutional authorization agreement.

The list of IRBs designated by the Institutional Official as the IRBs relied upon by the Human Research Protection Program and the scope of review of these IRBs is available in the Office of Regulatory Compliance.

3.4.1 The Criteria for use of an External IRB

This organization may rely upon the IRB of another organization so long as the other organization has an active FWA and has IRB Policies and Procedures available for review, provided one of the following is true:

- The IRB is the IRB of an AAHRPP accredited organization.
- This organization’s investigator is a collaborator on Human Research that is primarily conducted at another organization and the investigator’s role does not include interaction or intervention with subjects.

- The organization is engaged in the Human Research solely because it is receiving federal funds. (Employees and agents of the institution do not interact or intervene with subjects, gather or possess private identifiable information about subjects, nor obtain the consent of subjects.)

- The university has a long standing relationship with the IRB, for example, CU Boulder

- The IRB is a signatory to SMART IRB

- The use of a central IRB is mandated by the funding agency..

If the IRB or their organization are not AAHRPP accredited, their policies and procedures for IRB review will be reviewed for compliance with applicable laws and regulations.

The IRBs relied upon by this organization have the authority to:

Approve, require modifications to secure approval, and disapprove all Human Research overseen and conducted by the organization. All Human Research must be approved by an IRB designated by the Institutional Official. Officials of this organization may not approve Human Research that has not been approved by the IRB.

Suspend or terminate approval of Human Research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

Observe, or have a third party observe, the consent process and the conduct of the Human Research.

Determine whether an activity is Human Research.

Evaluate financial interests of investigators and research staff and have the final authority to decide whether the financial interest and management plan, if any, allow the Human Research to be approved.

3.4.2 Existing Relationships with External IRBs

Since 2005, UCD has had a relationship with Western IRB (WIRB) to facilitate a centralized IRB approach to industry sponsored research but then broadened the range of external IRBs available in 2018

NCI CIRB is used by the UCD Cancer Center in accordance with NCI policies and procedures. DHHA also utilizes NCI CIRB via a relationship with Colorado Community IRB.

VA ECHCS uses the NCI CIRB for appropriate oncology protocols, the VA central IRB and other central IRBs when allowed by the VA.

UCD in collaboration with the affiliate hospitals has also entered into a number of memorandum of understanding and IRB Reliance Agreements to facilitate a centralized approach to IRB review for federally funded research.

Investigators may also request via the Portal application to cede to an external IRB. This mechanism will be considered for more than minimal risk research only as described earlier in this document.

3.4.3 Communications

The External IRB team liaison with the external IRB of record. Their role is to facilitate collection of study documents for UCD reference, manage the relationship with the external IRB and ensure coordination of the institutional responsibilities that frequently are maintained locally such as training requirements, HIPAA privacy board oversight, conflict of interest management and other regulatory committee approvals specific to the research anticipated.

The Associate Vice Chancellor for Regulatory Compliance or designee is responsible for maintaining the university relationship with the external IRBs. The Associate Vice Chancellor for Regulatory Compliance or designee will be responsible for reviewing and coordinating the investigation of issues of potential serious noncompliance or continuing noncompliance or unanticipated problems in coordination with the external IRB.

3.5 *COMIRB Office*

The COMIRB Office is the administrative support to the COMIRB and its respective panels.

The COMIRB Office reports to the Associate Vice Chancellor for Regulatory Compliance of UCD (who also serves as the Institutional Official and the Signatory Official on the Federal Wide Assurance for UCD). The Associate Vice Chancellor for Regulatory Compliance reports to the Vice Chancellor for Research and has expert knowledge in regulatory issues regarding human subjects, oversees the UCD Human Research Protection Program, and is the primary contact at COMIRB for the Office for Human Research Protections, Department of Health and Human Services.

The Director is a member of the staff of the Associate Vice Chancellor for Regulatory Compliance and has day-to-day responsibilities for the operation of the two UCD IRB offices. The main IRB Office is on the CU Anschutz Medical Campus but there is also a small office on the Denver Campus. This includes responding to faculty, student, and staff questions about human subject research as well as organizing and documenting the review process. The Director works closely with the Assistant Director, the Expedited/Exempt reviewers, and the Chairs of the panels in the development of policy and procedures.

Each panel at COMIRB has support staff: consisting of two or three panel coordinators, with administrative support.

The office has additional support personnel as outlined in the current organizational charts for the COMIRB office. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is formally evaluated on an annual basis.

3.6 *Colorado Law*

COMIRB relies on the counsel of the General Counsel of the University for the interpretation and application of Colorado State law and the laws of any other jurisdiction where research is conducted as they apply to human subject research.

The exception is research conducted by Eastern Colorado Health Care System which relies on the VA Regional Council for legal interpretation and implementation.

4 Relationships

4.1 *Relationship with UCD HRPP*

The COMIRB panels function independently of, but in coordination with, other institutional regulatory committees. Each panel, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected. The panels have review jurisdiction over applicable research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that has adopted the human subject regulations.

Panel S does not review any research conducted under the Food and Drug Administration (FDA) policy, and regulations at 21 CFR 50 and 21 CFR 56, or when the research will be conducted at one of the UCD affiliate sites. All such research must be submitted to one of COMIRB's biomedical panels for review.

Research that has been reviewed and approved by COMIRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has been disapproved by one of the COMIRB panels.

COMIRB has monthly Chairs meetings. Members include all the panel chairs, the Associate Vice Chancellor for Regulatory Compliance, the Director and Assistant Director of COMIRB, the Director, Institutional Privacy and Compliance Officer. Research compliance officers of affiliates served by COMIRB are invited on an ad hoc basis as appropriate. During the first part of the meeting, this committee acts as the Compliance Board for COMIRB in accordance with the review responsibilities established in section 20. The Chairs discuss IRB rosters, submission volume, consistency among the IRBs, new and ongoing issues, updates to COMIRB policies and procedures, and other concerns relating to COMIRB or the UCD HRPP. Training is also conducted at these meetings as needed.

All of the main components of the UCD HRPP have read-only access to the COMIRB database. This includes: the Clinical Research Administration, COIC program, G&C Office, IBC, RDRC.

COMIRB communicates directly with the IBC, RDRC and SARC to ensure the appropriate approvals have been obtained per institutional policy.

COMIRB partners with the Center for Bioethics on education initiatives and requests ethics consults on a protocol by protocol basis.

The Vice Chancellor for Research and the Associate Vice Chancellor for Regulatory Compliance (IO) meet monthly with the Directors that report directly to them (e.g., the Director of the COMIRB Office, the Director of Clinical Research Administration, the Institutional Compliance and Privacy Officer, the Environmental Health and Safety Director, and the Institutional Animal Care and Use Committee Director.)

The Vice Chancellor for Research and the Associate Vice Chancellor for Regulatory Compliance (IO) meet at least monthly for updates on any compliance issues. The AVC for Regulatory Compliance meets at least monthly with the Director of COMIRB to discuss any controversial protocols. The AVC for Regulatory Compliance (IO) then has an opportunity to determine if there is any research of concern to the institution.

The Director or designee of COMIRB is a voting member of the COIC Committee and acts as the liaison between the COIC program and the COMIRB panels.

Other officers of the UCD HRPP are invited to COMIRB panel meetings to discuss individual protocols on a case by case basis.

4.2 *Relationship with Affiliate's HRPP*

Each Affiliate has a mechanism for reviewing protocols that are to be submitted to COMIRB.

Each Affiliate's Compliance Office has read-only access to the IRB database, limited to protocols for which their institution is a performance site.

The Director of COMIRB is a non-voting member of the ECHCS R&D Committee.

The Associate Vice Chancellor for Regulatory Compliance and/or Director, COMIRB meet regularly with representatives of the Human Research Protective Program with each Affiliate. These meetings act to advise the Associate Vice Chancellor for Regulatory Compliance, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating compliance information to the research community.

4.3 *Relying Sites and Investigators*

COMIRB may choose, on a case-by-case basis, to provide IRB review for a non-affiliated institution or individual researcher. The Director decides whether COMIRB can serve as a lead or sIRB for other sites, in consultation with the IO. If the Director or IO does not believe COMIRB has adequate resources to ensure regulatory compliance for the non-affiliated site(s), the study team will need to identify an alternative IRB, either private or from another AAHRPP-accredited academic institution.

For IRB reliances, a formal agreement for IRB review and reliance must be established between the University and the other institution. When frequent IRB reliances are anticipated, this may be through a Memorandum of Understanding between the University and the relying institution(s). For single studies, the formal agreement will be executed under SmartIRB if possible, and if not, with an IRB Authorization Agreement (IAA). The IAA, SmartIRB agreement, or MOU all document the responsibilities of the relying organization and COMIRB under the reliance. An Individual Investigator Agreement is used for single investigators where another institution is not engaged in the research. These agreements plus COMIRB approval must be finalized before the external site or investigator is covered by COMIRB.

In the conduct of cooperative research projects, COMIRB acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations.

When COMIRB reviews research conducted at another institution, the particular characteristics of each institution's local research context must be considered, either through direct knowledge of its local research context by COMIRB, or through information provided by the relying institution and reviewed by the IRB.

When UCD is the coordinating center for a multi-center protocol, the COMIRB will require the local PI to ensure that IRB approval has been obtained at each participating site prior to initiation of the research at that site. At the time of initial review, the COMIRB will assess the procedures for dissemination of protocol information (e.g. unanticipated problems involving risks to participants or others, protocol modifications, interim findings) to all participating sites.

4.3.1 Process and requirements for reliance on COMIRB by a DoD institution

For DoD-supported research reviewed by COMIRB, the sponsoring DoD component's Human Research Protection Official (HRPO) must review and approve the research before it may begin, in addition to COMIRB approval. For DoD-conducted research in which a DoD institution relies on COMIRB for IRB review, an Institutional Agreement for IRB Review (IAIR) must be executed between the University and the DoD institution specifying that COMIRB will apply the requirements of DoDI 3216.02, and COMIRB must be maintain its registration in accordance with 45 CFR 46, Subpart E.

When a DoD institution relies on COMIRB for oversight, the local Principal Investigator is responsible for the following: submitting to the DoD component's HRPO documentation of IRB review and approval (including scientific merit review, amendments, and continuing reviews), documentation of key investigators' human research protection training, IRB-approved protocol documents, and the University's current FWA and IRB registration numbers; obtaining HRPO approval before initiating the research; and promptly notifying the HRPO of changes to key investigators or institutions, changes that decrease benefit or increase risk in greater-than-minimal-risk research, addition of vulnerable populations or DoD-affiliated personnel as subjects, transfer of IRB oversight, external investigations, unanticipated problems, suspensions or terminations, serious or continuing noncompliance, continuing review results, and study closure. For emergency medicine research subject to 10 USC 980, the Principal Investigator's responsibilities are described in Section 22.8.3.

5 COMIRB Panel Membership

5.1 *Roles and Responsibilities*

5.1.1 Chair of the COMIRB Panel

The UCD Institutional Official, in consultation and approval with the panel members, and the Director of the COMIRB Office, appoints a Chair of the panel to serve for renewable three-year terms. Any change in appointment, including removal, requires written notification.

The panel Chair should be a highly respected individual, from within the University, fully capable of managing the panel, and the matters brought before it with fairness and impartiality. The task of making COMIRB and each panel a respected part of the institutional community will fall primarily on the shoulders of the Chairs. Each panel must be perceived to be fair, impartial and immune to pressure by the institution’s administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources.

The panel Chair is responsible for conducting the meetings and is the signatory for correspondence generated by the COMIRB panel.

The panel meeting is chaired by one individual designated as a panel Chair. Most panels have two co-chairs and then one person is assigned as chair for the meeting but the role alternates between meetings.

The panel Chair may designate other panel members to perform duties, as appropriate.

The panel Chairs advise the Institutional Official and the Director of the COMIRB Office about panel member performance and competence at a yearly evaluation session and at the monthly Compliance Board meetings when appropriate.

The performance of the panel Chairs will be reviewed on an annual basis by the Director of the COMIRB Office in consultation with the Institutional Official. If the Chair is not acting in accordance with the COMIRB's mission, following these policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she will be removed.

5.1.2 Delegation of Chair of COMIRB Panel

A Chair on the roster of another panel or the Expedited/Exempt Chair can serve as the Chair of the panel in the absence of the designated Chair and has the same authority and duties as Chair but cannot count to quorum unless listed on the roster for that panel.

When the meeting Chair has a conflict of interest that will require them to recuse themselves from the discussion or vote on an individual protocol review, the other panel Co-Chair automatically assumes the responsibility of Chair for that particular review. If the other panel co-Chair is unavailable an attending panel member will be assigned responsibility for chairing the meeting for the review of that study.

5.2 *Appointment of Members to the COMIRB Panel*

The panel Chair and/or the Director of the COMIRB Office, identifies a need for a new or replacement member, or alternate member. The panel may nominate candidates and sends the names of the nominees to the COMIRB Office. Department Chairs and others may forward nominations to the Institutional Official, to the COMIRB Office, or to a panel Chair.

For faculty members, the Director of the COMIRB Office contacts the nominee. If there are no nominees, then appropriate Department Chairs or Program Directors will be contacted in writing by the Institutional Official, or the Director of the COMIRB Office, concerning the vacancies and solicit nominees from the Department Chairs or Program Director.

The final decision in selecting a new member is made by the Institutional Official, the panel Chairs, and the Director of the COMIRB Office. In order to ensure that the IRB panels are not compromised by competing business interests, individuals who have responsibility for business development cannot serve on the IRB or be involved in the day-to-day operations of the IRB. For example, the director of grants and contracts, the Vice Chancellor for Research, or deans of research who are responsible for raising funds or garnering support for research cannot serve as IRB panel members or be involved in the daily operations of the IRB.

Appointments are automatically renewed every three-years of service. Members may resign by written notification to the panel Chair or COMIRB Office.

Eastern Colorado Health Care System (ECHCS) VA Representatives. The Director of the **ECHCS** will officially appoint ECHCS VA representatives to the IRBs of record in writing. The ECHCS VA representatives will be appointed for a period of 3 years and may be re-appointed indefinitely.

On an annual basis, the panel Chairs and the Director of the COMIRB Office review the membership and composition of each panel to determine if they continue to meet regulatory and institutional requirements.

5.2.1 Alternate Members

The appointment and function of alternate members is the same as that for primary panel members, and the alternate's expertise and perspective are comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the panel when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the panel meeting that the primary member received or would have received.

The panel roster identifies the primary member(s) for whom each alternate member may substitute. The alternate member will not be counted as a voting member unless the primary member is absent. The panel minutes will document when an alternate member replaces a primary member.

5.2.2 Consultants

Consultant members are standing, non-voting members of the panel and have specific competence in special areas to assist in the review of issues or protocols, which require appropriate scientific or scholarly expertise beyond, or in addition to, that available on the panel. The appointment and initial training of consultant members is the same as for full board and alternate members, and consultant members must follow the same conflict of interest requirements as full board and alternate members. Consultant members are not subject to the same continuing education or meeting attendance requirements, as full or alternate members. The role of the consultant member is to serve as a non-voting member of the panel. Consultant members are assigned as primary reviewers according to the procedures described in Section 12.6. When a consultant member provides the primary review, the consultant member will receive and review the same materials prior to the panel meeting that the primary member received or would have received. Usually, consultant members are specialized and so their expertise are only needed on a limited basis due to the volume of potential protocols they can review (e.g., ophthalmology, orthopedics) or they are not able to commit the time to be a full board or alternate. Serving in the capacity of a consultant may also be part of the training phase in preparation for being an alternate.

The consultant member is not identified on the panel roster and will not be counted as a voting member. The panel minutes will document when a consultant member provides the primary review. The recommendations of the consultant member will be documented in the minutes along with the determination of the panel.

5.2.3 Use of Ad-Hoc Consultants (Outside Reviews)

When necessary, the Panel Chair or the Director of the COMIRB Office may solicit individuals from the University or the community with competence in special areas to assist in the review of issues or protocols, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the panel. The need for an outside reviewer is determined in advance of the meeting by the Director or the Chair by reviewing the protocols scheduled to be reviewed at the convened meeting. The COMIRB Office will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Information provided by ad-hoc consultants at meetings will be summarized in the minutes. Written reviews provided by the outside reviewer will be filed with the protocol.

The Director of the COMIRB Office (or designee) will contact the Conflict of Interest and

Commitment office to ensure that the ad-hoc consultant has a current conflict of interest disclosure on file. The Director or designee will then review the conflict of interest policy for panel members with ad-hoc consultants and ad-hoc consultants must verbally, or in written correspondence, confirm to the Director of the COMIRB Office or designee that they do not have a conflict of interest with the protocol prior to review. Individuals who have a conflicting interest or whose spouse or family members have a conflicting interest in the sponsor of the research will not be invited to provide consultation for that review.

The ad hoc consultant's findings will be presented to the full board for consideration either in person or in writing. If in attendance, these individuals will provide consultation but may not be a primary reviewer and may not vote.

5.3 *Duties of COMIRB Panel Members*

The agenda, submission materials, protocols, proposed informed consent forms and other appropriate documents are distributed to members prior to the convened meetings at which the research is scheduled to be discussed. Members receive the materials at least one week before each meeting, in order to participate fully in the review of each proposed project. Panel members and COMIRB staff will treat the research proposals, protocols, and supporting data confidentially. Any hardcopies of the protocols and supporting materials distributed at the meeting are returned to the COMIRB staff at the conclusion of the review for professional document destruction.

5.4 *Attendance Requirements*

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the Chair, or COMIRB Office staff member. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the Chair or the Director.

If a panel member is to be absent for an extended period of time, such as for a sabbatical, he or she must notify the panel Chair or COMIRB office at least 30 days in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the panel. If the member has a designated alternate, the alternate can serve during the primary member's absence.

Additional attendance requirements for panel Chairs, members and unaffiliated members are outlined in the SOP entitled "Training and Education" (CP-011).

5.5 *Training/Ongoing Education of COMIRB Chair and Panel Members*

A vital component of a comprehensive human research protection program is an education program for COMIRB Chairs and the COMIRB members. UCD is committed to providing training and an on-going educational process for COMIRB members and the staff of the COMIRB Office, related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

5.5.1 Orientation

Prior to beginning training as a prospective panel member, the trainee will be sent:

- A copy of the Belmont Report;
- UCD COMIRB Policies and Procedures for the Protection of Human Subjects (CP-001);
- SOP entitled "Training and Education" (CP-011);

- Member Information Sheet (CF-027)
- Link to the COMIRB website for more information on policies and regulations

New COMIRB members, including alternate members and consultant members will meet with the appropriate panel Chair, panel Compliance Officer, and/or Director of the COMIRB Office for an informal orientation session. New members are required to complete the Initial Education requirement for COMIRB members before they may serve as Primary Reviewer.

5.5.2 Initial Education

COMIRB members will complete the following web-based training:

- CITI Human Subject training (can include basic biomedical, basic social/behavioral, GCP and responsible conduct of research)
- CITI HIPAA Module; and

COMIRB members will also observe two panel meetings and conduct a mentored panel review as part of their training.

5.5.3 Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the COMIRB are consistent with current regulatory and policy requirements, training is continuous for COMIRB members throughout their service. Educational activities include, but are not limited to:

- Regular meeting attendance;
- Training workshops or webinars;
- Copies of appropriate publications;
- Identification and dissemination by the Director or designee of new information that might have affected the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to panel members via email, mail, or during panel meetings;
- Community persons annual education day (community members only)

The Associate Vice Chancellor for Regulatory Compliance will provide support to send as many members of the COMIRB as possible to attend the annual PRIM&R or AAHRPP conferences or regional OHRP conferences on human research protections.

The COMIRB Office Professional Staff is required to complete the entire CITI Course in the Protection of Human Research Subjects and the CITI HIPAA module. Staff will be expected to attend yearly educational lectures, webinars or workshops, and to attend PRIMR or OHRP training on a rotating basis.

COMIRB leadership is expected to become CIP-certified.

A description of how members and staff are trained and how training is tracked is outlined in Standard Operating Procedure-CP-011- “Training and Education”.

5.5.4 Additional training requirements

In the case that a funding agency (e.g., DoD) has additional training requirements for COMIRB Chairs, members or staff (e.g., proof of completed human research ethics and human subjects training), these requirements will be communicated to the COMIRB

Director or Assistant Director from the investigator (in consultation with the Program Officer) and in consultation with Office of Grants and Contracts as appropriate. Funding agencies may evaluate University human research ethics and human subjects training policies to ensure compliance with agency policies. In the case that a funding agency's training requirements for COMIRB Chairs, members of staff exceed those of the University (e.g., in terms of content or frequency of continuing education), COMIRB Chairs, members and/or staff will be required to complete the additional training and provide proof of completion to the funding agency.

5.6 *COMIRB Panel Member Conflicts of Interest*

Personal Conflicts of Interest are declared by all new panel members on the Member Information Sheet Form and then updated as necessary. Financial Conflicts of Interest are collected annually on all UCD faculty by the Conflict of Interest and Commitment Office in compliance with institutional policy. Non-UCD panel members and consultants are required to complete the same declaration with the Conflict of Interest and Commitment Office.

Panel member COI information is entered onto a tracking sheet and then any declared conflicts of interest will be managed by the coordinators and COMIRB Senior IRB staff when assigning protocols.

Additionally, members will be required to verbally make a conflict of interest declaration at the beginning of each meeting and declare any potential conflicts of interest at the beginning of the panel meeting for discussion and assessment in accordance with the Standard Operating Procedure-CP-020- "Management of panel member conflicts of interest".

Panel members and ad-hoc consultants will not participate in any panel action taken, including the initial and continuing review of any project, in which the member has a conflict of interest, except to provide information requested by the panel. Panel members are expected to self-identify conflicting interests. A primary reviewer or expedited reviewer with a conflict of interest must notify the COMIRB staff who will re-assign the protocol.

Panel members or consultants may find themselves in any of the following conflicts of interest when reviewing research:

1. Where the member or consultant is involved in the design, conduct, and reporting of the research.
2. Where a family member (defined as spouse/domestic partner and dependent children) of the member or consultant is involved in the design, conduct, and reporting of the research.
3. Where the member holds significant financial interests (See the UCD Procedure on Conflicts of Interest and Commitment's definition of significant financial interests) related to the research being reviewed.
4. Any other situation where the member or consultant believes that another interest conflicts with his or her ability to deliberate objectively on a protocol.

Except when requested by the panel to be present to provide information, panel members will absent themselves from the meeting room when the panel reviews research in which they have a conflict of interest. The Chair will allow for board discussion once the conflicted member has recused him/herself. The absent member is not counted toward quorum and his/her absence during the discussion and vote on the protocol will be noted in the panel meeting minutes.

If the Conflict of Interest status of a panel member changes during the course of a study, the Panel member is required to declare this to the panel Chair and/or Director of the COMIRB Office.

6 Panel Structure

6.1 *Composition of the IRB*

- Each COMIRB panel will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
- Each panel will 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 panel will be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. Each panel will therefore include persons knowledgeable in these areas.
- As the panel regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, individuals with impaired decision making capacity, students, employees, or economically or educationally disadvantaged persons), consideration will be given to the inclusion of one or more individuals on the panel, who are knowledgeable about and experienced in working with these subjects. When protocols involve vulnerable populations, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the panel or as consultants.
- In support of affiliates' ANCC Nursing Magnet accreditation, the IRB panels responsible for reviewing nursing research for UCHealth or CHCO must have a nurse present at the majority of convened meetings. These IRBs will include one nurse as a Primary voting member, and alternate nurses as appropriate. These IRB members will be appointed with the cooperation of nursing leadership at UCHealth and CHCO.
- Every nondiscriminatory effort will be made to ensure that each panel does not consist 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 panel on the basis of gender. Each panel shall not consist entirely of members of one profession.
- Each panel includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- Each panel includes 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. Each panel also has at least one member who represents the perspective of research subjects.
- Each panel designated as an "IRB of Record" for the VA Eastern Colorado Health Care System must include two or more VA Eastern Colorado Health Care System VA employees as voting members on the IRB roster(s) registered with OHRP. At least one of these members must have scientific expertise. The members must serve as primary members of the panel; this includes reviewing non-VA research matters coming before the panel. At least one of the VA members of the panel must be present during the review of VA research. [Specifically, Panel A, B and D have been designated as IRBs of Record for the VA Eastern Colorado Health Care System.]

- VA Research and Development administration officials including, but not limited to the Associate Chief of Staff for Research and Development and the Administrative Officer for Research and Development, are prohibited from serving as voting members of these panels.
- Physicians, dentists, nurses, pharmacists, social workers, other clinicians, statisticians, and allied health professionals are considered scientists.
- Veterans whose only relationship with the VA facility is receiving care at a VA facility or receiving benefits from the Veterans Benefits Administration are not considered to be affiliated with the VA for the purpose of being an IRB member.
- Individuals who perform occasional volunteer activities without compensation (WOC) are not considered affiliated with the VA. However, those who hold a WOC appointment for volunteer activities other than IRB service are considered to be affiliated. Individuals who have retired from the VA and who are receiving VA retirement benefits are considered affiliated with the VA.
- One member may satisfy more than one membership category.

6.2 *Liability Coverage of COMIRB Panel Members*

The University's insurance coverage applies to employees and any other person authorized to act on behalf of the University who perform acts or omissions within the scope of their employment or authorized activity.

6.3 *Undue Influence*

If a panel chair, panel member, or COMIRB staff person feels that the panel has been unduly influenced by any party, they shall make a confidential report to the Associate Vice Chancellor for Regulatory Compliance and/or the Vice Chancellor for Research, depending on the circumstances. The institution will conduct a thorough investigation and corrective action will be taken to prevent additional occurrences.

VA panel members and co-chairs can also contact the Denver VA medical center director to make a confidential report if they have experienced undue influence or if they have concerns about the IRB.

6.4 *Review of Panel Member Performance*

Immediate feedback for IRB members is encouraged at all IRB meetings, particularly positive feedback as appropriate. Feedback may be provided by the Chair, Compliance Officer, and IRB coordinators. The Panel Members' performance will be reviewed on an annual basis by the Director of the COMIRB Office in conjunction with the panel Chairs and COMIRB management. Members who are not acting in accordance with the COMIRB's mission or policies and procedures or who do not meet the minimum attendance requirements may be removed from the IRB or switched from Primary Member to Alternate. If individual members are identified as needing additional training or mentoring, COMIRB management and/or a panel chair will provide appropriate feedback and assess improvement. Review of IRB rosters takes place regularly at Compliance Board/Chair meetings.

6.5 *Review of COMIRB and COMIRB Office Performance*

The Office of Regulatory Compliance will conduct a performance audit of COMIRB processes and records on a regular basis. Results of these audits are provided to the COMIRB Director for discussion among COMIRB management. The COMIRB management formulates an improvement plan based on these results.The audit results, along with the improvement plan,

are distributed to the Associate Vice Chancellor for Regulatory Compliance or discussed at a COMIRB Compliance Board meeting.

6.6 *Evaluation of COMIRB Staff*

All COMIRB staff undergo formal performance evaluation annually, as required for all University staff. Job expectations are articulated in job descriptions and University evaluation instruments. All staff are managed and evaluated according to University HR policies.

6.7 *Resources for COMIRB*

The UCD Institutional Official (Associate Vice Chancellor for Regulatory Compliance) provides resources to the COMIRB and COMIRB Office, including adequate meeting and office space, and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines, will be made available to the panel and administrative staff. The resources provided for the COMIRB panels and COMIRB Office will be reviewed during the annual budget review process.

6.8 *Conduct of Quality Assurance/Quality Improvement Activities for COMIRB Operations and Active Research*

The Quality Assurance (QA) team will conduct quality assurance activities of COMIRB in accordance with its internal standard operating procedures. The COMIRB office uses the findings from these audits for quality assurance and, when necessary, to develop internal quality improvement initiatives.

7 COMIRB Records

The COMIRB office must prepare and maintain adequate documentation of the COMIRB's activities including: copies of all items reviewed, including, but not limited to research proposals, investigators' brochures and recruitment materials; scientific evaluations (if any) that accompany the proposals; DHHS-approved sample consent document and protocol, approved consent documents including HIPAA Authorization documents; any proposed amendments and the COMIRB action on each amendment; reports of unanticipated problems including serious and unexpected adverse events; documentation of protocol violations; and documentation of non-compliance with applicable regulations. The frequency of the next continuing review must also be documented.

COMIRB records must also include continuing review activities; copies of all correspondence between the COMIRB and investigators; progress reports submitted by investigators; reports of injuries to subjects and statements of significant new findings provided to subjects must be maintained with the related research proposal and, when reviewed at a panel meeting, must be documented in the minutes. The frequency of the next continuing review must also be documented.

COMIRB must also maintain a record of all unanticipated problems; unexpected adverse events submitted; and protocol violations submitted.

A resume for each COMIRB member and record of training must be maintained in accordance with the COMIRB training SOP.

Documentation of verified exemptions consists of the reviewer's written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exemption

category.

COMIRB records of IRB reviews must include: the specific permissible review category for expedited reviews; a description of action taken by the reviewer; and any determinations required by the regulations, including that criteria for approval are met when research is approved, and whether noncompliance is serious or continuing, and protocol-specific findings supporting those determinations.

COMIRB records must document any determinations required by the regulations and protocol-specific findings supporting those determinations including:

- Waiver or alteration of the consent process.
- Research involving pregnant women, fetuses, and neonates.
- Research involving prisoners.
- Research involving children.
- Research involving decisionally challenged subjects.

In addition, for VA research, COMIRB records must also include correspondence between the COMIRB and the Research and Development Committee.

For research subject to DoD oversight, COMIRB will make records that document compliance or noncompliance with DoD Instruction 3216.02 accessible for inspection and copying, as determined by DoD HRPP personnel, by authorized DoD representatives. The DoD may require submission of records be sent to the DoD for archiving.

7.1 *Reviewer Checklists*

Checklists are used at COMIRB to maintain consistency across the COMIRB panels and expedited review to help ensure that the deliberations of the panel are conducted in consideration of the regulations. The checklist represents the views of the reviewer utilizing the checklist for full-board reviews while the checklist represents the final documentation of IRB reviews for non full-board reviews. For full-board reviews, the minutes of the panel meeting (described below) describe the deliberations and final determinations of the panel. The appropriate primary reviewer checklist is used for initial review of a protocol with addendum checklist(s) as needed. The addendum checklist(s) may be completed by a separate reviewer from the primary reviewer depending on the expertise needed. For protocols reviewed at full board, A non-scientific review is also conducted on all initial reviews of protocols, and on subsequent reviews as necessary. Checklists include reminders about conflicts of interest.

7.2 *Minutes of a COMIRB Panel Meeting*

Proceedings must be written and available for review by the COMIRB Chair and panel at a subsequent meeting or electronically. Once approved by the COMIRB panel, the minutes must not be altered by anyone.

Minutes of COMIRB meetings must contain sufficient detail to show:

- The basis for requiring changes in research.
- The basis for disapproving research.
- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document (for example NCI or COG).
- The presence of a quorum throughout the meeting.
- Attendance at the meetings including those members or alternate members who are

participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions;
- Alternate members attending the meeting and for whom they are substituting;
- The initial attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect those members present for the entire discussion and vote on that item.
- Actions taken by the COMIRB including the basis or justification for these actions and any required changes in the research.
- The rationale for significant risk/non-significant risk device determinations (if applicable);
- Notification to COMIRB members of actions taken through expedited review and the expedited review category, and those studies that have been determined to be exempt from COMIRB review, indicate that the IRB members had an opportunity to ask questions or raise concerns, and summarize questions or concerns, if any, raised by the IRB members;
- Separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened COMIRB;
- Documentation that the required criteria [45 CFR 46.111] for IRB approval of research are met.
- Documentation that the research meets each of the required criteria [45 CFR 46.116(d)] along with protocol-specific information justify why the COMIRB considers the research to meet each criterion when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain informed consent;
- Documentation that the research meets each of the required criteria [45 CFR 46.117] along with protocol-specific information justifying why the COMIRB considers the research to meet each criterion when the requirements for written documentation of consent are waived;
- When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the COMIRB's protocol-specific justifications and findings regarding the determinations stated in the Subparts or the COMIRB's agreement with the findings and justifications as presented by the investigator on COMIRB forms.
- The vote on actions, including the number of members voting for, against, and abstaining;
- A note indicating that when a COMIRB member has a conflicting interest with the research under review, as defined by University policy, relative to the proposal under consideration that the COMIRB member was not present during the deliberations or voting on the proposal (and that the quorum was maintained);
- A written summary of the discussion of controverted issues and their resolution;
- Documentation that the investigator(s) has the appropriate background and experience to conduct the research. [Note: The IRB is not responsible for confirming that the investigator or other research team members have met current credentialing, privileging, and clinical training requirements.]
- Review and documentation of additional safeguards to protect vulnerable populations if entered as study subjects when this is not otherwise documented in COMIRB records including findings related to the use of surrogate consent;
- Documentation that safeguards are adequate to protect the rights and welfare of

subjects who are likely to be susceptible to coercion or undue influence.
- The determination of the level of risk.
- For initial and continuing review the frequency of continuing review of each proposal, as determined by the COMIRB;
- Documentation, when appropriate, that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data in accordance with the 45 CFR 46.111(a)(7) and HIPAA Privacy Rule.
- Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization;

7.2.1 Minutes for VA Research

Minutes of COMIRB meetings must contain documentation that:

- The approval of research contingent on specific minor conditions by the chair or designee, in the minutes of the first panel meeting that takes place after the date of the approval;
- Documentation justifying for inclusion of non-Veterans as subjects for protocols that are VA protocols;
- A summary of the discussion when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used for research purposes in the study. The summary must include the security measures that are in place to protect the SSN instances embedded in the study. [Note: This does not apply if the only use of SSNs is on the informed consent form, on the HIPAA authorization form as required by VHA Directive 1907.01, or for subject payment].
- In addition to documenting compliance with the HIPAA privacy rule, the minutes must take into consideration the requirements of 45 CFR 160 and 164, and other laws regarding protection and use of Veterans' Information, including the Privacy Act of 1974, 5 U.S.C 552a; VA Claims Confidentiality Statute, 38 U.S.C 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV), and Sickle Cell anemia Medical Records, 38 U.S.C 7332; and Confidentiality of Healthcare Quality Assurance review Records, 38 U.S.C 5705.
- Documentation that applicable VHA and VA information security policies pertaining to research are implemented.

Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

Minutes will be written and prepared within three weeks of the meeting date and made available for review. In preparing the minutes, the COMIRB compliance officer responsible for the meeting may include a "post-meeting compliance note" to help clarify any regulatory issues that remain vague following the committee's discussion. The post-meeting compliance notes are discussed with the responsible panel Chair for concurrence. If the post-meeting compliance change significantly impacts a decision made by the committee, panel concurrence may be required.

The COMIRB Minutes, once approved and signed by the Panel Chair, may not be altered by any persons of authority except by the COMIRB Chair, with the concurrence and approval of the convened panel on any points of alteration.

A copy of the COMIRB-approved minutes for each COMIRB meeting must be distributed to the Institutional Official, Affiliate and University counsel upon request. The

R&D Committee of the EASTERN COLORADO HEALTH CARE SYSTEM must be given a copy of the unredacted COMIRB-approved minutes to review for each VA-designated COMIRB panel.

7.3 *Membership Rosters*

A membership list of COMIRB members for each panel must be maintained; it must identify members sufficiently to describe each member's chief anticipated contributions to COMIRB deliberations. The list must contain the following information about members:

1. Name
2. Earned degrees
3. Affiliated or non-affiliated status (neither the member nor an immediate family member of the member may be affiliated with the university)
4. Status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist). For purposes of this roster, COMIRB members with research experience are designated as scientists. Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research. Students being trained in research fields will be designated as scientists.
5. Areas of experience, to describe each member's chief anticipated contributions to COMIRB deliberations.
6. Representative capacities of each COMIRB member; which COMIRB member is a prisoner representative (as required by Subpart C), and which COMIRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations locally involved in research.
7. Role on the COMIRB (Chair, Co-Chair, etc.)
8. The primary members or class of primary members for whom each alternate member could substitute.
9. Voting status (Any *ex officio* members are non-voting members)
10. Alternate status.
11. Relationship (e.g., employment) to affiliate organizations.

The COMIRB Office must keep each COMIRB membership roster current. The Director of the COMIRB Offices reports changes in COMIRB membership to the Compliance Board.

COMIRB IRBs are all registered with OHRP. Registration is renewed at least every three years. The IRB registration will also be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information and/or an IRB chair. The AVC for Regulatory Compliance, the COMIRB Director or COMIRB Assistant Director will serve as the contact person on the registration and is responsible for updating the IRB registration through the OHRP online system. The COMIRB Director is responsible for monitoring the IRB registration for renewal. The IRB registration expiration date is posted on the COMIRB web page.

7.4 *Records Retention Requirements*

The above detailed records must be stored securely by the COMIRB Office and must be retained for at least 10 years. Records involving exempt or non-human subject research activities will be retained for ten (10) years unless otherwise indicated by the researcher. The Research and Development Committee and the other affiliate hospitals have access to relevant COMIRB records.

Records pertaining to VA and greater than minimal risk research must be stored securely by the COMIRB Office and must be retained for at least 10 years after completion of the research. COMIRB records not associated with research will be retained at the facility for at least 10 years. If a protocol is closed without subject enrollment, COMIRB records will be retained for at least five years after closure.

After that time those records will continue to be kept securely or will be shredded or otherwise destroyed. All records must be accessible for inspection and copying by authorized representatives of the OHRP, FDA, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

Active records for VA and greater than minimal risk studies are maintained in file cabinets within locked offices within the COMIRB Office and are available only to COMIRB members and COMIRB office staff. Records for active and closed minimal risk, exempt, and non-human subjects research (if submitted to COMIRB) are stored electronically in a secure system, and may also be stored securely by an independent contractor off site.

For VA research only, in accordance with the National Archives and Records Agency (NARA) Records Control Schedule 10-1 (July 2015), Sequence Section #7.7 and #7.8**:**

COMIRB Protocol Files (RCS10-1, Sequence Section 7.7)**:** COMIRB files related to the review and oversight of research protocols submitted by VA investigators for research conducted at or by the VA ECHCS must be stored and retained for 6 years after the cut off (cut off is the end of the fiscal year [September 30th] following when the research project has been completed or terminated). During this retention period, COMIRB will maintain records of VA protocols in the InfoEd that can be accessed by the VA as needed. Prior to destruction, once this retention time requirement has been met, the VA ECHCS Research Office must be contacted and give concurrence. When this VA ECHCS concurrence has been received by COMIRB, the records must be disposed of promptly following NARA required procedures. A copy of the certificate of destruction must be sent to the VA ECHCS Administrative Officer/R&D. These records include, but are not limited to: the COMIRB application and attachments; the research protocol and amendments; case report forms; reports of adverse events, complaints, and deviations from the approved protocol; data and safety monitoring reports; research findings to date; and all relevant documents and related correspondence between COMIRB and the investigators in the review of an associated protocol.

For protocols disapproved by COMIRB or the VA R&D Committee, or withdrawn by the investigator, records related to the research project must be retained for 3 years after the cut off (cut off is the end of the fiscal year [September 30th] following when the research project has been disapproved or withdrawn). During this retention period, COMIRB will maintain records of VA protocols in the InfoEd that can be accessed by the VA as needed. Prior to destruction, once this retention time requirement has been met, the VA ECHCS Research Office must be contacted and give concurrence. When this VA ECHCS concurrence has been received by COMIRB, the records must be disposed of promptly following NARA required procedures. A copy of the certificate of destruction must be sent to the VA ECHCS Administrative Officer/R&D. These records include, but are not limited to: the COMIRB application and attachments; the research protocol and amendments; case report forms; reports of adverse events, complaints, and deviations from the approved protocol; data and safety monitoring reports; research findings to date; and all relevant documents and related correspondence between COMIRB and the investigators in the review of an associated protocol.

Files related to the ongoing operations of COMIRB (RCS10-1, Sequence Section 7.8) **:**

Implementation Records must be retained for 3 years after the cut off (cut off is the end of the fiscal year [September 30th] after the final action, expiration, or when superseded). During this retention period, COMIRB will maintain records of implementation records; they will be made available for review and/or copying to the VA upon request. Prior to destruction, once this retention time requirement has been met, the VA ECHCS Research Office must be contacted and give concurrence. When this VA ECHCS concurrence has been received by COMIRB, the records must be disposed of promptly following NARA required procedures. A copy of the certificate of destruction must be sent to the VA ECHCS Administrative Officer/R&D. Implementation records include, but are not limited to: agreements between the VA ECHCS and UCDenver for the use of COMIRB; standard operating procedures; policies and educational materials; documents assessing the effectiveness of COMIRB and compliance with all regulatory requirements; and related correspondence not related to specific protocols received or created during the course of COMIRB operation.

COMIRB Operations Records must be retained 6 years after the cut off (cut off is the end of the fiscal year [September 30th] after the final action, expiration, or when superseded). During this retention period, COMIRB will maintain records of COMIRB operation records; the documents will be made available for review and/or copying to the VA upon request. Prior to destruction, once this retention time requirement has been met, the VA ECHCS Research Office must be contacted and give concurrence. When this VA ECHCS concurrence has been received by COMIRB, the records must be disposed of promptly following NARA required procedures. A copy of the certificate of destruction must be sent to the VA ECHCS Administrative Officer/R&D. COMIRB operation records include, but are not limited to: membership rosters, appointment letters, curricula vitaes (CVs), training records, meeting minutes and related documentation.

Complete (non-redacted) minutes must be made available to the R&D Committee. COMIRB intends to provide non-redacted minutes except under special situations. In these cases non-redacted minutes will be provided upon request by the R&D Committee.

7.5 *Written Procedures and Guidelines*

The COMIRB Policies for Human Research Protection at UCD detail the policies and regulations governing research with human subjects.

The detailed requirements for submitting research proposals for review by the COMIRB are further detailed on the COMIRB website.

The detailed procedures for implementing the COMIRB Policies for Human Research Protection are outlined in the COMIRB Standard Operating Procedures, process mapping, instructions to investigators and guidelines.

These are not static documents. The UCD COMIRB Policies and Procedures for Human Research Protection are reviewed annually and revised by the Director of the COMIRB Office, the panel Chairs, and University counsel. The Associate Vice Chancellor for Regulatory Compliance will approve all revisions of the COMIRB policy document. The Director will approve all revisions to the COMIRB Standard Operating Procedures, process mapping and guidelines.

The COMIRB website and the COMIRB Standard Operating Procedures are reviewed at least annually and revised in accordance with the relevant standard operating procedure.

The details of how policies and procedures within COMIRB are changed is further detailed in SOP – “How to amend COMIRB policies, standard operating procedures, process mapping and

guidelines" (CP-019).

The Director of the COMIRB Offices will keep the University research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies, procedures and forms will be available on the COMIRB website and copies will be available upon request.

8 Human Subject Research Determination

The responsibility for the initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of "human subject" detailed in section 2.1.2 (DHSS) and 2.1.3 (FDA) of this policy document and "research" detailed in section 2.1.1 of this policy document and the other tools available on the COMIRB website. Since the University will hold them responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the COMIRB Office if there is any uncertainty. Informal requests may be made verbally, by phone contact, by email or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination. Informal requests represent the opinions of COMIRB personnel and are not formal endorsements of the project as Non-human Subject Research. The exceptions to this policy are detailed below.

If an investigator wants COMIRB to make a formal determination that research does not meet the definition of human subject research, this must be submitted formally to COMIRB for its consideration. Within the COMIRB Office, determination of human subject research may be made by experienced members of the COMIRB Office staff or any COMIRB panel member. Determinations are made according to whether the activity meets the definition of "research" and involves "human subjects" using a COMIRB Reviewer checklist. COMIRB staff will respond in writing to formal requests for determination of human subject research status. A copy of the submitted materials and determination correspondence will be kept on file.

Classroom projects do not have to be submitted to the IRB for review unless the project involves human subject research.

It is the responsibility of the faculty teacher, department and school to ensure that all activities conducted in the classroom that involve interaction with the public are conducted in accordance with ethical principles. The IRB is available as a resource to help students develop appropriate class resources but the school is ultimately responsible for their conduct.

Quality Assurance/Quality Improvement (QA/QI) projects and Program Evaluation (PE) projects can be evaluated by the department, school or affiliate using the QA/PE checklist to determine if the proposed project meets the definition of human subject research. Currently there are committees in place to make this determination at the Children's Hospital Colorado, College of Nursing Anschutz campus, and the School of Public Affairs and School of Education on the downtown campus, and at Denver Health and Hospital Authority. Otherwise, the investigator can self-certify that a project does not meet the definition of human subject research. Any project considered to potentially meet the definition of human subject research must be submitted to COMIRB for review. For any such project determined not to meet the definition of human subject research, the checklist should be signed by the researcher and the person within the department, school or affiliate that is making the determination. A copy of the determination

should be kept by the deciding authority or the researcher for future reference.

8.1 *Non-Human Subject Research which requires IRB review and approval*

If submitted to the IRB, COMIRB will consider whether private information or specimens for non – FDA purposes are not individually identifiable, when there is a direct or indirect link through a coding system, in accordance with OHRP "Guidance on research involving coded private information or biological specimens".

Private information or specimens do not meet the criteria for human subject if the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals and the investigators cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain because, for example:

- The investigators and the holder of the key have entered into an agreement prohibiting the release of the key to investigators under any circumstances, until the individuals are deceased. If submitted to COMIRB for a determination, a copy of this agreement should be submitted with the application.
- The data is coming from a data management center that has IRB-approved written policies and procedures prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased.
- There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This policy applies to existing private information as well as future collection for purposes other than the currently proposed research (e.g., medical records or on-going collection of specimens for a tissue repository).

9 Request for Exemption

Certain categories of research, exempt research, are not subject to federal regulations and do not require convened Institutional Review Board (IRB) review and approval. Research activities that meet the criteria set forth by the federal regulations [45 CFR 46.101(b) or 21 CFR 56.104 (c)(d)] and that involve minimal risk may qualify for exemption.

Investigators cannot self-exempt from review. Exempt research is subject to institutional review which has been delegated to COMIRB. All research that may meet the criteria for exemption to be conducted at UCD or an affiliate must be submitted to COMIRB for it to be reviewed and approved. Although exempt research is not covered by the federal regulations, this research is not exempt from UCD or the appropriate Affiliate's policies on responsible conduct of research or the ethical guidelines of the Belmont Report.

9.1 *Exemption of Eastern Colorado Health Care System Research*

Projects that are exempt from COMIRB review must be reviewed by the Eastern Colorado Health Care System R&D Committee prior to initiation and then they must be included in its annual review of research projects. For questions contact the VA Research Office.

9.2 *Limitations on Exemptions*

1. Research Involving Vulnerable Populations:

- **Children** [45 CFR 46.401(b) (2)]: Exemptions apply to children as research subjects with the exception of:
  - Exempt Category (2). This category only permits exemptions if the project involves educational tests or the observations of public behavior when the investigator does not participate in the activities being observed. Also, the provision for exemption with limited IRB review may not be used for research involving children.

    In other words, research involving children cannot be classified as exempt under Category (2) if the research involves:
    - Survey
    - Interview Procedures
    - Observations of public behavior when the investigator participates in the activities being observed.
  - Exempt Category (3). This category may not be used for research involving children.
- **Prisoners** [45 CFR 46.301(a)]: **Exemptions do NOT apply,** except for research aimed at involving a broader subject population that only incidentally includes prisoners
- **Other vulnerable populations:** Persons who are cognitively impaired, economically/educationally disadvantaged, pregnant, or are fetuses will be reviewed in consideration of their vulnerable status to determine eligibility for exempt status.

2. Food and Drug Administration (FDA) Regulated Research Exemptions: The following categories of clinical investigations are exempt from the requirements of COMIRB review:
   - 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 COMIRB review. [21 CFR 56.104(c)] Note: See FDA section for a detailed discussion of this exemption.
   - 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. [21 CFR 56.104(d)]

9.3 *Categories of Research Permissible for Exemption*

To receive an exempt determination, a protocol must satisfy the criteria under one of the following exemption categories. The limitations of one category do not prevent a protocol from being exempt under another category. For example, research on educational methods in children that uses surveys or interviews to collect data specifically to evaluate the educational methods tested can be considered exempt under Category (1).

Except for the limitations described above, the following categories are eligible for exemption:

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.

- "Commonly accepted settings" usually involve schools but also includes non-academic settings where education of patients, professionals, clients or other populations is commonly conducted.
- Participation in research should not be a required part of the curricula. Students should be able to refuse participation without penalty.

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:

   (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 45 CFR 46.111(a)(7).

   If the research involves children, the research is eligible for exemption under this category only if the research is limited to educational tests and/or observations of public behavior when the investigators do not participate in the activities being observed, and only under the conditions in (A) or (B).

   The reviewer may request that the Investigator provide an "Invitation to Participate" to potential participants when appropriate. The Invitation is an explanatory letter that may include: an explanation of the research project; the duration of participation time; information on how to contact the investigator; a statement indicating anonymity or confidentiality; and an indication that the return of the questionnaire will constitute the subject's consent to participate (a statement of voluntariness).

3. 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 §ll.111(a)(7).

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.

Examples of benign behavioral interventions eligible for exemption include having participants 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.

If the research involves deceiving the participants 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.

The reviewer may request that the Investigator provide an "Invitation to Participate" to potential participants when appropriate. The Invitation is an explanatory letter that may include: an explanation of the research project; the duration of participation time; information on how to contact the investigator; a statement indicating anonymity or confidentiality; and an indication that the return of the questionnaire will constitute the subject's consent to participate (a statement of voluntariness).

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:

   (A) The identifiable private information or identifiable biospecimens are publicly available;
   (B) 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;
   (C) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under HIPAA (i.e., 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
   (D) 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, and conducted in compliance with 45 CFR 46.104(d)(4)(iv).

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;
    - 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.

    For VA studies: The determination of exempt status for research and demonstration projects meeting the criteria for exempt category 5 must be made by the Under Secretary for Health on behalf of the Secretary of VA, after consultation with Office of Research and Development (ORD), Office of Research Oversight (ORO), Office of General Counsel (OGC), and other experts, as appropriate.

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

    This category applies to two different criteria.

    The first criterion applies to research involving wholesome food without any additives. An example would be a taste-test on different types of oranges from different parts of the country, using normal agricultural practices that do not involve the addition of food additives or chemicals.

    The second criterion applies to research on human subjects who consume plants or animals raised for food products.

    The FDA has determined levels of safety for various agricultural chemicals, referred to as GRAS (generally recognized as safe) and GRAE (generally recognized as effective) additives which are fed to animals raised for food production. If these additives are given to animals at or below the levels found to be safe by the FDA, the research is eligible for exemption.

    There are also approved levels for environmental contaminants set forth by the FDA, EPA, or the Food Safety and Inspection Service that may affect the grass or grain consumed by grazing food animals such as pesticides sprayed on a field. If the research involves taste testing of food products that come from animals exposed to contaminants and the investigator can demonstrate that the level of contaminants is at or below the approved levels, then the research can be exempt.

9.4 *How to Submit an Exempt Application*

Investigators must submit the COMIRB Application Form that includes the following information:

1. Problem to be studied
2. Description of the research methods
3. Description of the subject population
4. Expected date of completion
5. Plan for protecting privacy and confidentiality
6. A copy of the proposal if the research is externally funded
7. Supporting documents such as data collection tools, surveys, and Invitation to Participate.
8. For VA studies only: Affirmation that a master list will be maintained by the PI for all subjects for whom informed consent will be obtained in the study or documentation that maintaining names on such a master list poses a potential risk to the subjects from a breach of confidentiality;

Investigators will submit the Exempt Application to COMIRB to determine whether the protocol meets the criteria for exemption. The PI must endorse the submission through the PI Attestation form (see section 25.2.3).

9.5 *COMIRB Exempt Review Process*

The exempt review process is identical to the expedited review process (see section 11.2). That is, all exempt reviews are conducted by a panel Chair or designated COMIRB panel member who is an IRB member, all exempt submissions are evaluated for adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, and all exempt approvals are reported to an IRB.

Reviewers may make the exemption determination, conduct Limited IRB Review, HIPAA privacy determination, request clarifications/ modifications, or refer the project for review in another research category.

The reviewer will determine whether additional measures are needed to protect the rights and welfare of the research participants. Although there is no regulation requiring informed consent for exempt research, the reviewer may request all or some of the elements of informed consent be included in a consent process, script or document.

A COMIRB Reviewer checklist will be used for reference for exempt determinations. The applicable determinations will be documented in the COMIRB approval letter.

COMIRB will respond in writing with the reviewer's determination.

Exemptions are not assigned an expiration date. After five years, COMIRB will issue a closure report to the investigator; the investigator must respond to this notice to maintain an active exempt project.

Amendments to Exempt Research

9.6 *Additional Protections in Exempt Research*

Although exempt research is not covered by the federal regulations, this research is not exempt from UCD and COMIRB policies on responsible conduct of research or the ethical guidelines of the Belmont Report.

9.7 *Exemption of VAMC Research*

Projects that are exempt from COMIRB review must be reviewed by the VAMC R&D Committee prior to initiation and then they must be included in its annual review of research projects.

10 When sites are Engaged in Research

10.1 *Categories of sites Engaged in Research*

[follows OHRP- guidance on Engagement of Institutions in Human Subject Research, October 16, 2008]

10.1.1 Sites are considered engaged in human subject research if:

a. The institution receives an award through a grant, contract or cooperative agreement from HHS for non-exempt human subjects research, even if all activities involving human subjects are carried out by employees or agents of another institution.
b. Employees or agents from the institution perform invasive or noninvasive procedures
c. Employees or agents from the institution intervene for research purposes with a subject of the research by manipulating the environment
d. Employees or agents from the institution interact for research purposes with any subject of the research.
e. Employees or agents from the institution obtain the informed consent of human subjects
f. Employees or agents from the institution obtain for non-exempt research purposes identifiable information or identifiable biological specimens from any source. This can include observing or recording private behavior, using, studying or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

For VA research, including exempt: If an outside firm (e.g., a survey research firm) is contracted to obtain consent from participants, collect private individually identifiable information from human participants, or be involved in activities that would institutionally engage the firm in human participants research, it is considered engaged and must have its own IRB/EC oversight of the activity.

10.1.2 Sites are considered to be not engaged in human subject research if:

a. Employees or agents from the institution perform commercial or other services provided all of the following:
    - The services performed do not merit professional recognition or publication privileges;
    - The services performed are typically performed for non-research purposes; and
    - The employees or agents of the institution do not administer any study intervention being tested or evaluated
b. Employees or agents from the institution provide clinical trial-related medical

services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met:

- The institution's employees or agents do not administer the study interventions being tested or evaluated under the protocol;
- The clinical trial-related medical services are typically provided by the institution for clinical purposes; the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and when appropriate, investigators from an institution engaged in the research retain responsibility for overseeing protocol-related activities; and ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

c. Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (e.g., an oncologist at the institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided all of the following conditions also are met:

- An investigator from an institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol;
- The institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;
- Investigators from the institution engaged in the research retain responsibility for: i) overseeing protocol-related activities; (ii) ensuring the study interventions are administered in accordance with the IRB-approved protocol; and (iii) ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; and an IRB designated on the engaged institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution not selected as a research site.

d. Institutions whose employees or agents can inform prospective subjects about the availability of the research; provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects' consent for the research or act as representatives of the investigators; provide prospective subjects with information about contacting investigators for information or enrollment; and/or seek or obtain the prospective subjects' permission for investigators to contact them.

e. Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another institution.

f. Institutions whose employees or agents release, to investigators at another institution, identifiable private information or identifiable biological specimens pertaining to the subjects of the research.

g. Institutions whose employees or agents: (i) obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and (ii) are unable to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:
    - The institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to those employees or agents under any circumstances;
    - The releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution's employees or agents under any circumstances; or there are other legal requirements prohibiting the release of the key to the institution's employees or agents.

    Coded means that:

    (i) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); and
    (ii) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

    Note that in some cases the institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the institution releasing such information or specimens should: (a) ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or (b) if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB's determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d). COMIRB may request copies of the informed consent documents used to obtain the original specimens in order to make its own determination that the proposed study is consistent with the original consent.

11 Expedited Review of Research

11.1 *Categories of Research Eligible for Expedited Review*

[follows 63 FR 60364-60367, November 9, 1998]

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

- The categories in this list apply regardless of the age of subjects, except as noted.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review — expedited or convened — utilized by the IRB.

The **Initial** expedited review procedure may not be used:

- Where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- For classified research involving human subjects
- For research involving major deception that will mislead subject about their health status, the researchers, or the research purpose
- For research involving the use of proxy consent or emergency waiver of consent
- For research requiring a device risk determination

11.1.1 Categories Pertaining to Initial Review

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required. (Note: Research on marketed devices that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8

week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.

Examples:

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

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

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

Non-invasive procedures will be reviewed in consideration of the impact the testing will have on the population. For example, exercise testing in a debilitated elderly population may exceed the minimal risk threshold.

5. Research involving materials (data, documents, records, or specimens) that have

been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

Projects that involve the collection of prospective data are reviewed via an expedited mechanism. Projects that collect identifiers, track data extraction through links, or use identification keys also fall under this category. If the information involved is sensitive or could be damaging, a full board review may be required.

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

As above, if the data collection involves sensitive or potentially damaging information, a full board review may be required. The reviewer will request a description of the plan to protect, store, and, in some cases, destroy recordings made for research purposes. This may include a plan for stripping identifiers from the data set or disguising identifying characteristics in recorded voices or images.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b) (2) and (b) (3). This listing refers only to research that is not exempt.]

If the data collection is studying the traits of specific populations, a full board review may be required if the findings could be stigmatizing to a segment of society. The reviewer will request a description of the plan to protect and store the data. This may include a plan for stripping identifiers from the data set.

11.1.2 Categories Pertaining to Continuing Review

8. Continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; *or*

(b) Where no subjects have been enrolled and no additional risks have been identified; *or*

(c) Where the remaining research activities are limited to data analysis.

Note: for category 8a the following applicability criteria apply:

(1) The remaining activities must be minimal risk,

(2) If identification of the subjects or their responses will reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, reasonable and appropriate protections will be implemented so that risks related to invasion

of privacy and breach of confidentiality are no greater than minimal, and
(3) The research may not be classified research.

For category 8b the only applicability criterion is that the research may not be classified research.

For a multi-site protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8) (a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Key features of expedited review under Category (9) include: i) the research is not conducted under an investigational new drug application (IND) or investigational device exemption (IDE); ii) the project does not meet the requirements for one or more of the expedited review categories (1-7); and iii) the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk.

The determination that "no additional risks have been identified" at each subsequent continuing review does not need to be made by the convened IRB.

If a research protocol has been initially approved through a full-board review procedure, and it was not found by the convened panel to be eligible for expedited review under categories 1 – 7, the continuing review may **not** be done by the expedited review procedure unless it falls within Category 8 or 9, above.

11.1.3 Categories Pertaining to Changes in Approved Research

Greater than minimal risk research:

Minor changes in research approved by a full board, during the period (of one year or less) for which approval is authorized, can be reviewed using the expedited review procedure.

A minor change is one which <u>does not</u>, in the judgment of the COMIRB reviewer:

(i) Significantly increase the overall risk of the study;

(ii) Significantly alter the research design or methodology; or

(iii) Significantly reduce protections for subjects.

Minimal risk research:

Any change made to research that has been determined to be minimal risk and eligible

for expedited review can be reviewed using the expedited review procedure, except for: 1) any change that poses greater than minimal risk to subjects; or 2) any change that would otherwise warrant review of the proposed changes by the convened panel. Note: adding procedures that are not eligible for initial expedited review would generally require full board review.

11.2 *Expedited Review Process*

Expedited Review means that the Application has been reviewed by a panel Chair or designated COMIRB panel member, rather than at a convened IRB meeting.

Chairs or designated reviewers who have a conflict of interest with the study will not participate in the review of that research.

The COMIRB Director or panel Chair approves the designation of the Expedited/Exempt reviewers. Designated reviewers are COMIRB panel members. They must have at least one year of IRB experience or commensurate research or regulatory experience. Reviewers undergo training in Expedited/Exempt procedures. Training includes mentored or supervised reviews.

The COMIRB Office staff evaluates each submission and assigns a primary reviewer with appropriate scientific, scholarly, regulatory or other expertise to conduct an in-depth review of the submission.

Reviewers will evaluate whether research is eligible for review using the expedited procedure by considering whether the research:

- Completely satisfies one or more Expedited or Exempt categories of research for initial or continuing review
- Does not require full board review
- In the case of amendments, involves no more than a minor change to the approved research
- For VA studies only: Affirmation that a master list will be maintained by the PI for all subjects for whom informed consent will be obtained in the study or documentation that maintaining names on such a master list poses a potential risk to the subjects from a breach of confidentiality

The reviewer will use appropriate Reviewer Checklists to guide their review (e.g., Primary Reviewer Checklist, Modification Checklist, Continuing Review Checklist, vulnerable population checklist) to determine whether the research meets the criteria for expedited review procedures and, if so, whether the research can be approved.

In reviewing the research, the reviewers may exercise all of the authority of the COMIRB panel except that the reviewers may not disapprove the research. If the reviewer believes that there is reason for disapproval, or the nature of the project is not suitable for expedited review, then the reviewer(s) must defer any decision and refer the application for review at a convened panel meeting.

In the event that expedited review is carried out by more than one reviewer and the reviewers disagree, the COMIRB staff will work to obtain a consensus. At the discretion of the COMIRB Director, Expedited/Exempt reviewer or panel Chair the protocol will be submitted to the panel for full board review.

Reviewers will indicate approval, approval with administrative changes, require modifications,

classify the project as Exempt, or Not Human Subject Research or defer to full board. If modifications are required COMIRB staff will inform the investigator by e-mail and/or letter. The response to modifications will be returned to a Chair or designated reviewer for further review. A response to approval with administrative changes can be reviewed by a COMIRB staff member to confirm that the changes were completed. COMIRB staff will notify researchers of the Reviewer's determinations in writing.

11.3 *Period of Approval*

At the time of initial review and at continuing review, the reviewer will make a determination regarding the frequency for continuing review. Protocols subject to pre-2018 regulation require continuing review no less than annually. Although continuing review is not required by regulation for expedited protocols subject to the 2018 requirements, continuing review may be required at the discretion of the reviewer. In some circumstances, a shorter review interval (e.g., annually) may be required. Reviewers will use the appropriate review checklist to document and justify the period of approval. The feedback letter will reflect the approval period.

11.4 *Informing the COMIRB Panel*

The COMIRB panel will be apprised of expedited review approvals through inclusion of this information on the panel meeting agenda under a section entitled "Submissions reviewed and approved under expedited procedures". Expedited review determinations are reported at least monthly at a designated panel meeting. Copies of all expedited approvals are available for optional review at the request of any panel member. An approval of research by expedited procedures does not require any ratification by the convened panel; however, the panel has the opportunity and authority to re-review previously approved expedited research at its discretion.

12 COMIRB Full Board Review Process

12.1 *Convened COMIRB Panel Meetings*

Except when an expedited review procedure is used, the COMIRB must review proposed research at convened panel meetings (also known as **Full-Board meetings**) at which a **quorum** (see below) is present.

12.2 *Schedule of COMIRB Panel Meetings*

In general, each panel meets twice a month on a regular basis throughout the year. Meeting schedules may be adjusted to accommodate public holidays. A meeting may also be cancelled due to lack of quorum. A special meeting may be called at any time by the panel Chair or the Director of the COMIRB.

12.3 *Quorum*

A quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a physician must be included in the quorum. The panel Chair, with the assistance of the COMIRB staff, will confirm that an appropriate quorum is present before calling the meeting to order. The panel Chair, with the assistance of the COMIRB staff, will be responsible to ensure that the meetings remain appropriately convened.

Votes may only occur when a quorum is present and documented as present by the Panel

Coordinator. The Panel Coordinator takes note of arrivals and departures of all members and notifies the chair if a quorum is not present. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated. In order for the research to be approved, it must receive the approval of a majority of those voting members [without a disclosed conflict of interest] present at the meeting.

IRB meetings are scheduled for attendance in-person. However, if a member cannot physically attend, they will be considered present if participating through teleconferencing or videoconferencing. In this case the member will have received all pertinent material prior to the meeting and is able to participate actively and equally in all discussions.

12.4 *Pre-Meeting Distribution of Documents*

Place and time of meeting is set forth on the cover sheet distributed to all panel members with their materials.

The review assignments will be emailed to all panel members approximately one week prior to each meeting. Once the review assignment is received, the panel members will be able to access all protocols and supporting documentation to be reviewed from InfoEd., The final agenda for the meeting is available at the meeting.

12.5 *Guests*

At the discretion of the panel, the Principal Investigator may be invited to the panel meeting to answer questions about their proposed or ongoing research. The Principal Investigator may not be present for the discussion or vote on their research.

Other guests may be permitted to attend panel meetings at the discretion of the COMIRB panel Chair and the Director of the COMIRB Office. Guests may not speak unless requested by the panel and must sign a confidentiality agreement.

The compliance officers for each Affiliate are non-voting members of COMIRB. In this capacity, each affiliate has access to the COMIRB database, applicable protocol documents and as needed act as the liaison between COMIRB and the Affiliate Institution.

12.6 *Primary Reviews*

The COMIRB Office staff evaluates each protocol and assigns a primary reviewer with appropriate scientific or scholarly expertise to conduct an in-depth review of the protocol. For initial reviews, or when requested by the panel, a non-scientific reviewer is also assigned. When making reviewer assignments, COMIRB staff ensures that when the IRB review research that involves subjects likely to be vulnerable to coercion or undue influence, at least one IRB member knowledgeable about or experienced in working with such subjects will be present at the meeting and assigns that individual to complete the addendum vulnerable population checklist(s).

If COMIRB Staff cannot identify a primary reviewer with appropriate expertise, the panel Chair or the Director of the COMIRB Office will solicit ad-hoc consultants from the University or the community with competence in special areas to assist in the review of issues or protocols, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the panel (see “Ad-hoc Consultants,”).

Before the meeting, each protocol application (including background information, project protocol, and informed consent) is reviewed by all panel members.

If there is not appropriate scientific / scholarly or representational expertise available then the

COMIRB staff will defer to another meeting or IRB, or obtain consultation.

At the meeting, the Primary Reviewer presents an overview of the goals, design, study procedures, safety procedures, and qualifications of the investigators and leads the panel through the completion of the regulatory criteria for approval using the COMIRB Primary Review checklist(s) appropriate for the type of review (initial, continuing, amendment). For initial full review, the assigned non-scientific reviewer also presents an overview of the study and leads the panel through the study and consent form using the Non-Scientific review checklist (CF-136).

12.7 *COMIRB Office Internal Review*

Applications are screened by the COMIRB Office staff for completeness. The Coordinator may return an incomplete submission to the PI to obtain any missing documents before placement on a full board agenda.

12.8 *Materials Received by the COMIRB*

For initial review each panel member receives and reviews the following documentation:

1. Complete Protocol Application form
2. Research Protocol
3. Proposed Consent / Parental Permission / Assent Form(s)
4. Recruitment materials / subject information
5. Data collection instruments (including all surveys and questionnaires)
6. HIPAA Authorization Forms
7. Conflict of Interest Management plan as proposed by COIC committee (when applicable)
8. Other relevant information

All investigators named on the application form must have a current curriculum vitae or biosketch on file with COMIRB. For Principal Investigators “in training” (students and fellows) a signed copy of the “Responsibilities of Students” document must also be submitted.

At least one primary reviewer must receive and review all the documents listed above as well as: any related grant applications; the sponsor’s protocol (when one exists); the investigator’s brochure (when one exists); the DHHS-approved sample informed consent document (when one exists); the complete DHHS-approved protocol (when one exists).

If a panel member requires additional information to complete the review they may contact the investigator directly or may contact the COMIRB Office to make the request of the investigator.

Protocol reviewers will use the appropriate Primary Review Checklist(s) as a guide to completing their review. As well as the primary reviewer checklist there are additional specific checklists to be used if the protocol involves vulnerable populations, devices, and / or is following Department of Defense (DoD) regulations and requirements or the Department of Education (DoE) regulations and requirements.

When a protocol is reviewed by the expedited procedure, reviewers are provided and are expected to review all information that the convened panel would have received using the same checklists. For expedited review protocols, any panel member can request to review the full protocol file by contacting the COMIRB Office.

If some or all of the study is to be conducted out of state then the PI is required to provide documentation to support the appropriate definition of “legally authorized representatives”, “children” and any other state law relevant to the IRB determination. The COMIRB staff will then

validate the information by either checking the source documents or contacting university legal counsel. For all states, “guardian” is defined as either the parent or person who has the legal right to make health care decisions for another.

Research to be conducted under the jurisdiction of the DoD shall undergo scientific review and the review is considered by the IRB. The PI must provide evidence of this approval with the initial submission (scientific review and approval by the CCTSI Scientific Advisory Review Committee or CIC PRMC does suffice for this requirement but must occur prior to IRB review).

Possible COMIRB Panel Actions Taken by Vote

12.8.1 Approval

The study is approved as submitted, or with minor consent or advertisements/subject materials changes administratively made by the COMIRB Office (“Approved with red-line changes” or "Approved with Administrative Changes").

12.8.2 Approved with Minor Modifications

Study documents require changes, based on the committee's understanding of the research, in order to meet the approval criteria under 45 CFR 46.111 (and/or 21 CFR 56.111) and ensure that human subject protections are adequate. Provided that these changes are made as requested, the committee finds that the research meets the criteria for approval. The needed revisions are agreed upon by the committee at the meeting. These revisions are presented to the Principal Investigator for incorporation by simple concurrence. The COMIRB Panel Chair only may approve the study upon receipt and approval of the revisions without further action by the panel; the Chair may exercise limited discretion in determining when an investigator has satisfactorily made each change requested, based on the committee's discussion of the issue.

Minor application form changes, confirmation of training, and/or confirmation of receipt of standard letters (e.g., IAAs) designated by the reviewer (e.g., "Approved with Administrative Changes") can be confirmed and approved by COMIRB staff. For Exempt/Expedited and Full Board reviews, COMIRB staff may administratively change an Approval decision to Minor Modifications required in order for the staff to ensure and verify completion of educational or COI requirements.

Note: Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the panel.

For studies conducted at the Eastern Colorado Health Care System, the research may not begin until the COMIRB Chair or designee has approved the changes and the Eastern Colorado Health Care System R&D Committee has approved the study.

12.8.3 Deferred for Substantive Issues

Substantive issues regarding the protocol and/or consent form must be addressed. This action is taken if substantial clarification is required, or insufficient information is provided for the committee to determine that all of the criteria for approval under 45 CFR 46.111 (and/or 21 CFR 56.111) have been met, and that human subjects are otherwise adequately protected. COMIRB approval of the proposed research must not occur until subsequent review of the revised material by the convened panel.

If the submission is deferred the following will occur:

1. The COMIRB Office informs the investigator in writing of the panel's decision, questions and concerns.
2. The investigator's response is sent to the COMIRB Office.
3. In order to receive approval for a deferred protocol, it must be submitted for full panel review at a subsequent, convened meeting of the same COMIRB panel. The COMIRB Office provides the panel with the investigator's response, the revised protocol with highlighted changes. The item is placed on the agenda for the following meeting.
4. The protocol application is given full panel review again.
5. If the panel had previously determined that fundamental changes were required, the Primary Reviewer's checklist is used. If the committee had clarification questions only then the deferral feedback letter is utilized as a checklist.
6. The outcome of the panel's deliberations is once again communicated to the investigator in writing.
7. The panel's determination concerning the subsequent amended submission will be documented in the minutes of that meeting.

12.8.4 Denied

Questions are of such significance that the panel feels approval of the study is unwarranted. Approval of a previously disapproved protocol requires full COMIRB panel review.

12.8.5 Approval in Principle [45 CFR 46.118]

There are certain circumstances in which the COMIRB may grant, after expedited or full board review (depending on the study procedures under review), approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to 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.

The panel may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests.

Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects. Full board continuing review may be required once human subjects are to be enrolled in the study, depending on the level of risk.

12.8.6 Appeals

If the COMIRB makes a decision by full board or expedited review that the investigator believes to be unduly restrictive, the investigator may appeal to the full board COMIRB

panel. The procedure for appeals is discussed in section 12.17.

12.9 *Other Considerations*

12.9.1 Determination of Risk

At the time of initial and continuing review, the panel will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either “minimal” or “greater than minimal” based on the definition of minimal risk. The meeting minutes will reflect the Committee’s determination regarding risk levels.

Additional risk determinations will also be made to fulfill obligations under subparts B, C or D as needed. (See section on vulnerable populations)

12.9.2 Period of Approval

At the time of initial review and at continuing review, the panel will make a determination regarding the frequency of review of the research protocols. All protocols will be reviewed by the COMIRB panel at intervals appropriate to the degree of risk. Research which does not require continuing review under the 2018 Regulations, 45 CFR 46.109(f), will not be assigned an expiration date unless a specific rationale for continuing review is provided. Research which requires full board continuing review, or which requires at least annual review due to external policies, will be reviewed no less than once per year. In some circumstances, a shorter review interval (e.g. semiannually, quarterly, or after accrual of a specific number of participants) may be required. The meeting minutes will reflect the panel’s determination regarding review frequency.

12.9.3 Review More Often than Annually

The following factors are considered when determining which studies require review more frequently than on an annual basis:

1. Significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
2. The involvement of especially vulnerable populations likely to be subject to coercion (e.g., institutionalized psychiatric patients, incarcerated minors);
3. A history of serious or continuing noncompliance on the part of the principle investigator.
4. The probability and magnitude of anticipated risks to subjects.
5. The likely medical condition of the proposed subjects.
6. The overall qualifications of the Responsible Investigator and other members of the research team.
7. The specific experience of the Responsible Investigator and other members of the research team in conducting similar research.
8. The nature and frequency of adverse events observed in similar research at this and other institutions.
9. The novelty of the research making unanticipated adverse events more likely.
10. Any other factors that the panel deems relevant.

In specifying an approval period of less than one year, the panel may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period,

it is understood that the approval period in no case can exceed 1 year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than 1 year.

12.9.4 Independent Verification Regarding Material Changes

Protecting the rights and welfare of subjects sometimes requires that the COMIRB verify independently, utilizing sources other than the investigator, information about various aspects of the study including but not limited to adverse event reporting, information in the scientific literature, reports of drug toxicity, drug approval status, and that no material changes occurred during the COMIRB-designated approval period.

The panel will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. Protocols where concern about possible material changes occurring without COMIRB approval have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by Principal Investigators who have previously failed to comply with Federal regulations and/or the requirements or determinations of the COMIRB.
3. Protocols randomly selected for internal audit.
4. Whenever else the COMIRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

- The probability and magnitude of anticipated risks to subjects.
- The likely medical condition of the proposed subjects.
- The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

In making determinations about independent verification, the COMIRB may prospectively require that such verification take place at predetermined intervals during the approval period, may retrospectively require such verification at the time of continuing review or may require such verification at any time during the approval period in the light of new information. Verification will be conducted in conjunction with the UCD or Affiliate Compliance Office.

12.10 *Consent Monitoring*

In reviewing the adequacy of informed consent procedures for proposed research, the panel may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the COMIRB has identified problems associated with a particular investigator or a research project.

12.11 *Conflicts of Interest*

UCD encourages and supports outside interactions of its faculty and student employees with federal, state and local governments, and with the business community and industry as

important parts of their research, education and public service activities. Since outside interactions also carry with them an increased potential for conflict of interest and/or commitment, either actual or perceived, UCD has developed procedures for identifying potential conflicts through annual disclosure, and ensure rigorous and consistent review of such disclosures.

12.11.1 General Conflict Management

To meet the above stated goals, UCD has centralized the Conflict of Interest and Commitment (COIC) Management program within the Office of Regulatory Compliance. A standing committee is charged to review the annual disclosure forms submitted by faculty and employees and to make recommendations on how to manage, mitigate or eliminate individual conflicts of interest and commitment as they arise in accordance with its standard operating procedures.

The UCD Office of Conflict of Interest and Commitment database triggers automatically a flag in the COMIRB database under personnel when an investigator or coordinator has a Significant Financial Interest (SFI). The IRB staff coordinate with the COIC staff to ensure that the financial conflict is considered in light of the new protocol. A recommendation is made by the COIC as to the appropriate components of a management plan for that particular protocol but the final determination regarding the management is made by the COMIRB when the study involves human subjects. Final approval of an initial or continuing review submission will not be granted until: 1) the principal investigator and all co-investigators and research personnel (except for personnel with the role of "Administrator") have completed their annual COI disclosure to the UCD office, and 2) it has been verified that there are no SFIs that could affect the protocol, or any SFIs that could affect the protocol have had a COI management plan approved by the IRB.

The Full Board (or IRB Chair, if the protocol was previously determined to represent minimal risk to subjects and be eligible for expedited or exempt review) will review the conflict management plan to determine if the conflict will adversely affect the protection of human subjects and if the management plan is adequate. Based on the significance of the conflict and the potential adverse effects on the protection of subjects, conflict management plans can include:

- Disclosure to subjects through the consent process;
- Modifications in the research plan and data analysis plan;
- Monitoring by independent reviewers;
- Divestiture of financial interests;
- Appointment of a non-conflicted Principal Investigator; or
- Prohibition of the conduct of research at UCD.

For research conducted in VA facilities, the VA financial conflict of interest form will be used and a management plan developed in accordance with VA policies and procedures. The VA management plan will be submitted to COMIRB for review and approval.

12.11.2 COMIRB Actions on COI Management Plans

The Full Board (or IRB Chair) can:

- Approve the management plan; or
- Request changes in the management plan, and approve the plan with those

changes; or
- Request changes in the management plan, and defer review until a revised plan is received; or
- An IRB Chair reviewer may refer the review to the Full Board.

A copy of the final, approved conflict management plan will be kept on file in the IRB Offices, as well as in the Office of Regulatory Compliance. The COMIRB panel coordinator will send the COIC office a copy of any revisions made to the draft COI management plan.

Any changes to the VA conflict of interest management plan will be sent to the DMVA research office.

12.11.3 Protocol-Specific Conflict Management

The COIC database flags in the COMIRB database when any investigators or key personnel have a declared significant financial interest. Investigators are also asked to self-identify SFIs on the Application for Protocol Review.

As part of its review process, the IRB panel will make a determination as to whether the conflict adversely affects the protection of human subjects. If the answer is yes and an approved conflict management plan exists, the IRB panel will review to determine if it adequately protects the human subjects in that protocol.

If no approved conflict of interest management plan exists, the IRB panel will refer the investigator(s) to the COIC Management Program and an appropriate conflict management plan will be developed according to the procedures described above.

Review of conflict management plans are documented in the panel minutes for full board review and in the protocol file for expedited review. If a conflict of interest exists, final IRB approval should not be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place.

If the conflict of interest status of an investigator or key personnel changes during the course of a study, the individual is required to notify the IRB Office and the COIC Office within 30 days of the change. The IRB panel will review the change as a modification to the protocol.

At the time of continuing review, the investigator and key personnel will be asked whether there has been any change in the conflict of interest status relating to the research. The IRBs panel will review conflict of interest as part of its continuing review.

UCD defines Institutional Conflict of Interest in the COIC policies and procedures document. Where institutional conflicts may arise from royalties or intellectual property rights associated with a technology that is the subject of the research, UCD manages these potential institutional conflicts of interest as an extension of the individual conflict of interest on a protocol specific basis. UCD has integrated the institutional conflict of interest management program with its existing program that has been described herein.

12.12 *Other Committee Approvals*

In the protocol application the investigator will be asked specific questions to determine if the research requires approval from other pertinent research compliance committees (Radioactive Drug Research Committee, Institutional Biosafety Committee, etc.). If the investigator answers yes to any of the questions, then they will be requested to provide documentation of approval from the other committees. Final approval from the COMIRB will be contingent on receipt of the

required documentation from the other regulatory or institutional committees.

In the protocol application, the investigator will be asked specific questions to determine if the research requires specific site approval (Portal clearance for University of Colorado Denver, University of Colorado Hospital, and Children's Hospital of Colorado; VA Clearance for Eastern Colorado Health Care System; SPARO acknowledgement for Denver Health). If the investigator answers yes to any of the questions, then they will be requested to provide documentation of approval from the other committees. Final approval from the COMIRB will be contingent on receipt of the required documentation (see section 12.16).

12.13 *Reporting COMIRB Actions*

All COMIRB actions are communicated to the Principal Investigator (PI), or designated primary contact person for the protocol, when possible in writing within fourteen (14) working days via a template letter prepared by the COMIRB staff. For an approval, along with written notification of approval, a copy of the approved consent form containing the stamped approval with the dates of the approval and expiration will be sent to the investigator. For a deferral, the notification will include the modifications required for approval along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision.

All letters to investigators must be filed in the protocol files maintained by the COMIRB office.

The COMIRB reports its findings and actions to the institution in the form of its minutes, which are available for review by the UCD Institution Official or delegates from the Affiliates and are stored permanently and securely in the COMIRB Office.

For research conducted within the Eastern Colorado Health Care System, COMIRB notifies the PI and the Eastern Colorado Health Care System R&D Committee in writing of its decision to approve or disapprove a proposed research activity, or of revisions required to secure COMIRB approval.

12.14 *Further Review/Approval of COMIRB Actions by Others within the Participating Institution*

Research that has been approved by COMIRB may be subject to further appropriate review and approval or disapproval by officials of the participating institutions; however, but those officials may not approve research if it has been disapproved by the COMIRB.

Required UCD approvals are generally coordinated prior to IRB submission as part of the portal review process. However, UCD reserves the right to subject research reviewed by COMIRB to further review.

Approval Required by Affiliates:

- When an affiliate institution is engaged in research, it must be indicated as a performance site on the COMIRB Application, regardless of whether subject interventions are occurring at the site.
- A COMIRB-approved research activity may be disapproved by the Eastern Colorado Health Care System R&D Committee, the Director of the Eastern Colorado Health Care System, or the Office of Research and Development. If a research activity is disapproved by the COMIRB, the decision cannot be overruled by the Eastern Colorado Health Care System R&D Committee, or any higher authority. The Eastern Colorado Health Care System R&D Committee and higher authority may strengthen

requirements and/or conditions, or add other modifications to secure Eastern Colorado Health Care System R&D approval or approval by a higher authority. Previously approved research proposals and/or consent forms must be re-approved by the COMIRB before initiating the changes or modifications requested by the Eastern Colorado Health Care System R&D.

- University Hospital requires additional approval by the UCH Research Support Office. If UCH requires additional changes to the protocol or consent, the Principal Investigator has to submit an amendment or update to address the issues of concern.
- Denver Health and Hospitals. COMIRB approval is always contingent on Denver Health Sponsored Programs and Research Office (SPARO).
- The Children's Hospital Research Institute coordinates and oversees all research at Children's Hospital Colorado in accordance with Children's Hospital Colorado policies. Any changes are coordinated with the PI prior to submission to COMIRB. If the Research Institute requires additional changes to the protocol or consent, the Principal Investigator has to submit an amendment or update to address the issues of concern.

12.15 *Appeal of COMIRB Decisions*

If a subcommittee of a panel makes a decision that the investigator believes to be unduly restrictive on the proposed research, the investigator may appeal, in writing, for review by the convened appropriate COMIRB panel.

If the convened COMIRB panel makes a decision that the investigator believes to be unduly restrictive on the proposed research, the investigator should first discuss the matter with the Chair of the relevant panel or the Director of the COMIRB Office, taking care to explain the reasons for believing that the proposed procedures are in compliance with University policy and with Federal regulations. If the issue cannot be resolved satisfactorily by negotiation, the investigator may appeal the decision of the panel, in writing. The panel will reconsider the appeal based upon the new information provided and will continue to re-review protocols as long as the investigator wishes to appeal.

12.16 *Sponsored Research Contracts*

All funded human subjects research must be reviewed and approved by an appropriate IRB. COMIRB is responsible for ensuring congruency between a funded grant and submitted IRB protocol. The external IRB coordinator is responsible for conducting a similar review if the protocol is reviewed by an external IRB.

Proposals to be submitted for external funding are sent to the UCD Office of Grants and Contracts (OGC) along with the Proposal Transmittal Form. OGC Staff review the compliance checklist on the Proposal Transmittal form to determine if the "human subjects" box is checked. If it is checked for human subjects, the OCG staff notify the PI that if the proposed research is funded, IRB approval must be received prior to establishing the grant account. If the human subjects box is not checked the OGC staff review the abstract or the statement of work to determine if the project involves human subjects. On occasion, OGC staff will contact the COMIRB (or other affected Compliance Offices) to determine appropriate follow up action. If it is determined that the proposed research involves human subjects the PI is reminded to obtain IRB approval and the account is not established until IRB approval has been obtained.

COMIRB, and Clinical Research Administration (CRA) use standard language to ensure consistency between the proposal document and the protocol. If CRA is negotiating a change to the standard language then the AVC for Regulatory Compliance or delegate and the Affiliate

Compliance Office are notified. If COMIRB is asked to significantly deviate from the standard injury and compensation language by a sponsor, consultation with the appropriate contracting office is required to ensure consistency with the contract.

The OGC Office and CRA has access to the COMIRB database and records so as to check the consent form against the grant or contract. The CRA is responsible for conducting a final congruency check between consent and contract language before notifying the affiliate that the protocol is approved if the contract is being managed by UCD. Any discrepancies are reported back to IRB and the PI. A change form must be submitted by the PI to correct the discrepancy.

Denver VAMC R&D committee reviews all COMIRB approved consents. Any required changes are reported back to COMIRB and the PI. An amendment or update form must be submitted by the PI to make the required changes.

Denver Health and Children's Hospital Colorado obtain copies of the final approved consent form from the PI to be checked against the grant or contract. Any discrepancies are reported back to COMIRB and the PI. A change form must be submitted to correct the discrepancy.

To facilitate study oversight at each institution, the compliance office for each institution is given access to the electronic system to be able to view only studies where that institution is listed as a performance site.

13 Criteria for IRB Approval of Research

In order for the COMIRB to approve human subject research it must determine that the following requirements are satisfied (45 CFR 46.111):

- 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.
- 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 COMIRB 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 COMIRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the COMIRB 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, individuals with impaired decision making capacity, or economically or educationally disadvantaged persons.
- 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 45 CFR 46.116.
- Informed consent will be appropriately documented, or documentation will be appropriately waived, in accordance with, and to the extent required by 45 CFR 46.117.
- When appropriate, the research plan makes adequate provision for monitoring the

data collected to ensure the safety of subjects.

- When appropriate, including when COMIRB is functioning as a privacy board under HIPAA, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects 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, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- Evaluate that the investigator(s) has the appropriate background and experience to conduct the research. [Note: The IRB is not responsible for confirming that the investigator or other research team members have met current credentialing, privileging, and training requirements.]
- When the researcher is the lead researcher of a multi-site study, evaluate appropriate protection of participants is in place. This evaluation should include:
    - Appropriate communication and reporting of unanticipated problems involving risks to participants or others;
    - Plan to manage interim results;
    - Plan to manage protocol modifications

For VA research:

- The approval of research contingent on specific minor conditions by the chair or designee, in the minutes of the first panel meeting that takes place after the date of the approval;
- Determine, when appropriate, justification for inclusion of non-Veterans as subjects for protocols that are VA protocols;
- Determine when real Social Security Numbers (SSNs), scrambled SSNs, or the last four digits of SSNs will be used in the study. The summary must include the security measures that are in place to protect the SSN instances embedded in the study. [Note: This does not apply if the only use of SSNs is on the informed consent form or the HIPAA authorization as required by VHA Directive 1907.01].
- In addition to determining compliance with the HIPAA privacy rule, the minutes must take into consideration the requirements of 45 CFR 160 and 164, and other laws regarding protection and use of Veterans' Information, including the Privacy Act of 1974, 5 U.S.C 552a; VA Claims Confidentiality Statute, 38 U.S.C 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV), and Sickle Cell anemia Medical Records, 38 U.S.C 7332; and Confidentiality of Healthcare Quality Assurance review Records, 38 U.S.C 5705.
- Determine that applicable VHA and VA information security policies pertaining to research are implemented.
- For VA multi-site research:
    - The PI and all local site researchers must obtain written approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other federal requirements.
    - Research cannot be initiated at any given site until the local researcher has obtained written notification that the research can be initiated from the local associate chief of staff for research and development.
    - The Privacy Officer must determine that there is appropriate authority to allow the disclosure of individual names and other information to any contracted

firms engaged in human subject research.

When following Department of Justice regulations, for National Institute of Justice (NIJ) funded research:

- All projects are required to have a privacy certificate approved by the NIJ Human Subjects Protections Officer.
- All researchers and research staff are required to sign employee confidentiality statements, which are maintained by the responsible researcher.\

The following responsibilities belong to the investigator:

- For National Institute of Justice-funded research, a copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
- At least once a year, the researcher shall provide the chief, Office of Research and Evaluation, with a report on the progress of the research.
- At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.
- In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
- The researcher shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

For research conducted with the Bureau of Prisons:

- The research will be conducted consistent with requirements of Federal Bureau of Prisons Program Statement 1075.01
- The selection of participants within any one organization must be equitable.
- Incentives may not be offered to help persuade inmate participants to participate. However, soft drinks and snacks to be consumed at the test setting may be offered.
- Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research participants who are both:
- No longer in Bureau of Prisons custody.
- Participating in authorized research being conducted by Bureau employees or contractors.
- A non-employee of the Bureau may receive records in a form not individually

identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.

- Except as noted in the consent statement to the participant, the researcher must not provide research information that identifies a participant to any person without that participant's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
- Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
- If the researcher is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint project involving ORE, the researcher may be asked to provide ORE with the computerized research data, not identifiable to individual participants, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.

For research conducted with the Department of Energy (DOE):

- COMIRB will use the "Checklist for IRBs to Use in Verifying that HS Research Protocols Are in Compliance with DOE Requirements" to ensure that the protocol is in compliance.
- COMIRB does not review DOE classified research or research at DOE sites.

For research conducted or supported by the Environmental Protection Agency (EPA):

- All human subjects research conducted or supported by the EPA must either be approved or be acknowledged as exempt research by the EPA Human Subjects Research Review Official (HSRRO) before any work involving human subjects research can begin. To obtain approval or a concurrence of exemption by the HSRRO, researchers must submit the IRB-approved research package or documentation of exemption, including evidence of IRB approval and any correspondence between the IRB and the researchers. See 40 CFR 26 and EPA Order 1000.17A.

For research not conducted or supported by any federal agency that has regulations for protecting human research participants and for which the intention of the research is submission to the EPA:

- EPA extends the provisions of the 40 CFR 26 to human research involving the intentional exposure of non-pregnant, non-nursing adults to any substance.

For research conducted under ICH-GCP (E6):

If this stipulation is accepted in the contract, then the Clinical Trial Contract Associate will notify the research team and COMIRB. The COMIRB panel will then use the addendum checklist to ensure the protocol is reviewed to comply with E6.

The Clinical Trial Contract Associate will also notify the Clinical Research Support Center Staff.

The COMIRB will also:

- Consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.
- Ensure that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.
- Ensure that the investigator should promptly report to the IRB/IEC: (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects;
- New information that may affect adversely the safety of the subjects or the conduct of the trial.
- Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning: (a) Its trial-related decisions/opinions. (b) The reasons for its decisions/opinions. (c) Procedures for appeal of its decisions/opinions.
- Records The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).
- Provide when asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

13.1 *Risk/Benefit Assessment*

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the COMIRB must:

- Judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the COMIRB - involves a series of steps:

- **Identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
- Determine whether the risks will be minimized to the extent possible;
- **Identify the probable benefits** to be derived from the research and assess the importance of the knowledge to be gained;
- **Determine whether the risks are reasonable in relation to the benefits** to subjects, if any;
- Ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits.

13.2 *Risks to Subjects are Minimized*

- By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; **and**
- Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

13.3 *Risks to Subjects are Reasonable in Relation to Anticipated Benefits*

- In evaluating risks and benefits, the COMIRB 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 COMIRB 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.

13.4 *Scientific Merit*

In order to assess the risks and benefits of the proposed research, the COMIRB must determine that:

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.
- The available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial (when following ICH-GCP (E6)).

In making this determination, the COMIRB may draw on its own knowledge and disciplinary expertise. All investigator-initiated, more than minimal risk protocols that have not received a full peer review are reviewed by the CU Anschutz Scientific Advisory Review Committee (SARC). NIH-funded protocols and other protocols that have received prior peer review undergo an expedited scientific review process. Major scientific changes to a protocol post peer review, will also be reviewed by SARC. SARC is a committee of experienced investigators, biostatisticians, and ethicists. The purpose of SARC is to evaluate the scientific merit of research protocols for the campus. COMIRB can also request a scientific review by SARC if significant scientific changes are requested relating to an approved protocol.

13.5 *Selection of Subjects is Equitable*

The COMIRB will review the recruitment methods and inclusion/exclusion criteria for the research to ensure equitable selection of subjects. In making this assessment the COMIRB takes into account the purposes of the research and the setting in which the research will be conducted, and is particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, fetuses, pregnant women, human in vitro fertilization, persons who are decisional challenged, or persons who are economically or educationally disadvantaged (see Vulnerable Populations).

13.6 *Recruitment of Subjects*

Potential subjects cannot be specifically contacted until COMIRB approval for the research has been obtained. It is possible to obtain general data relating to the availability of a specific population to ascertain the feasibility of the study.

There are a number of ways to recruit subjects:

- Clinical Relationship
- Existing research relationship
- HIPAA A Authorization
- Recruitment database

- Advertisements

13.7 *Students as Subjects*

When UCD students and/or employees are being recruited as potential subjects, researchers must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Researchers must emphasize to subjects that neither their academic status nor grades or their employment will be affected by their participation decision.

To minimize coercion, investigators should avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes other than their own. When entering a classroom to recruit students and conduct research, e.g. administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

13.8 *Finders Fees and Incentives*

Finder's fees include any payment or gift to an individual who identifies a prospective subject.

Principal Investigators and research personnel may not individually receive incentive payments or finder's fees on a per participant basis. PIs may accept monetary rewards that are offered by the sponsor only after the research is closed to enrollment and only if the reward is directed to the research team as a whole (e.g. funds allocated for purchasing educational materials or to support attendance at educational conferences).

Note: For faculty and staff employed by the Denver VA: Questions regarding finder's fees and incentives involving VA studies should be directed to the Denver VA Research Office or VA regional counsel.

13.9 *Advertisements*

Except as described in Sections 13.9.1 and 13.9.2, COMIRB must approve any and all advertisements prior to posting and/or distribution. The COMIRB may review:

- The information contained in the advertisement,
- The mode of its communication,
- The final copy of printed advertisements, and/or
- The final audio/video taped advertisements.

This information should be submitted to the COMIRB with the initial application or as an addendum to the protocol.

The COMIRB reviews advertising materials to assure that they are accurate and reasonable. Advertisements should not include misleading statements such as the following:

- Statements implying a certainty of favorable outcome or other benefits,
- Claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation,
- Claims, either explicitly or implicitly, that the test article was known to be equivalent or superior to any other drug, biologic or device,
- Using terms like "new treatment," "new medication," or "new drug" without explaining that the test article was investigational,

- Promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation,
- Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media,
- Does not include exculpatory language, and
- Offers by the sponsor to include a coupon good for a discount on the purchase price for the product once it has been approved for marketing.

13.9.1 Advertising Components Form

The COMIRB Advertising Components Submission Form (CF-260) is a document intended to present a variety of statements that may be used in advertising. COMIRB will review and approve the advertising components provided by the study team. Once approved, the study team may mix and match the components for advertising without additional review of the final ads by COMIRB.

13.9.2 Advertising Reviewed by Operational or Regulatory Partners

COMIRB works in partnership with other operational and/or regulatory offices who review advertising for the university or our affiliate health systems. For example, the Clinical Research Operations and Services team under the Vice Chancellor for Research at Anschutz Medical Campus, consults with study teams to create advertising campaigns and materials. Other examples are the RECRUIT and Patient Experience services at UCHealth. These partners have the same standards as COMIRB to make sure advertising is accurate and reasonable and does not include misleading statements. Advertisements approved by these partners are acceptable to COMIRB and do not require additional review by COMIRB.

13.10 *Payment to Subjects*

Payment to research subjects is a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

The panel must review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive.

13.11 *Informed Consent*

The COMIRB will ensure that 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 45 CFR 46.116 and 21 CFR 50.20. In addition, the Committee will ensure that informed consent will be appropriately documented, or documentation will be appropriately waived, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. See section 14 for a detailed discussion of informed consent requirements.

13.12 *Data Safety Monitoring*

The COMIRB will review the data safety monitoring plan for protocols involving more than minimal risk during initial review and at continuing review.

The data and safety monitoring plan for prospective studies must include, but is not limited to, the following:

a. What safety information will be collected;

b. How the safety information will be collected (e.g. with case report forms, at study visits, by telephone calls with subjects)

c. The frequency of data collection including when safety data collections starts;

d. If not using a DMC, and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;

e. Provisions for the oversight of safety data (e.g. by a DMC, Safety Officer or PI)

f. Conditions that trigger an immediate suspension of the research, if applicable

g. A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being; and

h. A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.

The data and safety monitoring plan for retrospective studies must include, but is not limited to, the following:

a. Monitoring for and reporting any breach of confidentiality.

For DoD regulated research, a medical monitor should be appointed when appropriate for studies involving more than minimal risk to subjects.

13.12.1 Differentiating Usual Care from Research

The COMIRB ensures that the PI has clearly identified the "usual care" aspects of the study from any research interventions. Usual care is what the subject would experience if s/he was not in the study. Usual care may be limited to one 'arm' of the study or is being delivered to all subjects as part of the study. Usual care components can become research procedures if the protocol dictates their delivery (including timing, dose, or choice of treatment), rather than the delivery decisions being made within the patient-provider relationship.

When a study involves 'usual care,' COMIRB ensures that the investigator must clearly designate the individual or entity responsible for relevant aspects of both the research and the usual care.

The COMIRB ensures that subjects will be able to identify which activity is research, and which is usual care, and know who (the researcher or the subject's health care provider) is responsible for:

a) Explaining potential risks and benefits of the treatment or service to the subject;
b) Providing the treatment or service;
c) Monitoring the treatment or service, as applicable;

d) Defining whether the adverse events result from usual care or research, as applicable;
e) Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered disk, a product recall); and
f) Documenting the subject's clinical course while receiving the treatment or service, as applicable

13.12.2 Enlisting Clinical Expertise

The COMIRB ensures that the investigator provides for clinical expertise. If the investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to:

a) Reviewing the data, adverse events, and new study findings; and
b) Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject).

13.13 *Privacy and Confidentiality*

At the time of initial review, the COMIRB ensures that the privacy of research subjects and confidentiality of research data are protected. The COMIRB assesses whether there are adequate provisions to protect subject privacy and maintain confidentiality. The COMIRB does this through the evaluation of the methods used to obtain information:

- About subjects,
- About individuals who may be recruited to participate in studies
- The use of personally identifiable records and
- The methods to protect the confidentiality of research data.

The PI will provide the information regarding the privacy of subjects and confidentiality of data at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The COMIRB will review all information received from the PI and determine whether or not the privacy of subjects and confidentiality of data are sufficiently protected. In some cases, the COMIRB may also require that a Certificate of Confidentiality be obtained to additionally protect research subjects and data (See Section 26.1).

13.13.1 Definitions

Privacy - having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.

Private information - information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Identifiable information – information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information directly or with a key to a code.

13.13.2 Privacy

The COMIRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the COMIRB must obtain information regarding how the investigators are getting access to subjects or subjects' information and the subjects expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

a. Methods used to identify and contact potential participants
b. Settings in which an individual will be interacting with an investigator
c. Appropriateness of all personnel present for research activities
d. Methods used to obtain information about participants and the nature of the requested information
e. Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey)
f. How to access the minimum amount of information necessary to complete the study.

13.13.3 Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the COMIRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

13.14 *Vulnerable Populations*

The COMIRB determines if appropriate additional safeguards are in place to protect the rights and welfare of subjects if they are likely to be members of a vulnerable population (e.g., persons with diminished autonomy).

13.15 *Information Security*

The COMIRB determines if an appropriate information security plan is in place.

1) For VA research only: This plan will also need to be reviewed and approved by the ISO. Any concerns of the ISO will be forwarded to COMIRB for consideration.

The plan must clearly identify, and include, but not be limited to:

a) Whether or not individually identifiable information is to be collected or used;
b) How the data is to be collected or acquired;

c) Where the data (original and all copies) is to be stored and corresponding security systems;
d) How the data is to be transported or transmitted from one location to another;
e) Who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security);
f) All entities or individuals outside VHA to whom the data is to be disclosed, and the justification for such disclosure and the authority (e.g., the HIPAA authorization);
g) Who is to have access and be responsible for the security of the information (e.g., the Coordinating Center, the statistician, and PI who has ultimate responsibility);
h) Mechanisms used to account for the information;
i) Security measures that must be in place to protect individually identifiable information if collected or used; and
j) How and to whom a suspected or confirmed loss of VA information is to be reported.

2) Providing for Reuse of Data

The COMIRB determines if the data may be reused in other studies, by reviewing:

- The research data repository plan outlining where and how the data is to be stored;
- The research informed consent and HIPAA authorization(s) associated with the protocol or the request for these to be waived. If COMIRB does not waive the requirements then the informed consent and HIPAA authorization content must include language on the uses and disclosures of the data as defined in the protocol as well as information on how privacy and confidentiality will be maintained and how the data will be secured.
- If the creation and operation of the data repository is not included in the data collection protocol, there must be a separate COMIRB-approved protocol for the creation and operation of the data repository.

13.16 *Flagging medical records for VA Research*

COMIRB has determined that all protocols must be flagged in the VHA Health Record unless the study is limited to secondary data or specimen use only.

If a VA investigator thinks his/her study should not be required to flag subject medical records, the investigator may request the ACOS/R recommend waiving the flagging requirement. If in agreement with the investigator's rationale, the ACOS/R will provide a letter to COMIRB that can be submitted with the protocol. An indication in the COMIRB feedback letter that CPRS flagging requirement has been waived alleviates flagging responsibilities for that study.

Note that by VA regulations, the mandatory flagging requirement will not be waived for studies that involve any of the following

- Any invasive research procedure;
- Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive;
- Clinical services that will be used in the medical care of the subject or that could interfere with other care the subject is receiving or may receive;
- The use of a survey or questionnaire that may provoke undue stress or anxiety.

Note: For studies that have a Certificate of Confidentiality the requirements for CPRS flagging is as follows:
i. For studies that do not involve a medical intervention, no annotation may be made in CPRS of this study

ii. For studies that involve a medical intervention, a progress note entry should indicate that the individual has been enrolled in a research study (in general terms), any details that would affect the individual's clinical care, and the name and contact information for the investigator conducting the study. Consent and HIPAA forms are not to be included in the health record.

14 Informed Consent

14.1 *Informed Consent Process*

No investigator may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the COMIRB. In general, the COMIRB considers individuals who are unable to consent for their own clinical care, as documented in the medical record, to be unable to consent for research participation. Direct evaluation of the subject, or tools/instruments such as the Mini Mental Exam can also be used to help determine capability to consent.

Investigators must obtain consent prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the COMIRB.

Consent must always be sought under circumstances that:

- Provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate; and
- Minimize the possibility of coercion or undue influence.

The COMIRB will consider where the consent process will take place and the individual who will be obtaining consent (e.g. the investigator, collaborator, or qualified designee) in its determination regarding the appropriateness of the consent process. When the potential participant's understanding of the research may be impaired due to the timing, location, or individuals participating in the proposed consent process, the COMIRB will require an alternative process.

The information that is given to the subject or the representative must be in language understandable to the subject or the representative.

The prospective subject or 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.

No informed consent, whether oral or written, may include exculpatory language which the subject or the representative is made to waive or appear to waive any of the subject's legal rights.

No informed consent, whether oral or written, may include exculpatory language through which releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

A person knowledgeable about the consenting process and the research (i.e., a member of the project's research team) to be conducted must obtain the informed consent.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity.

When following Department of Justice regulations:

- For National Institute of Justice funded research: a) the confidentiality statement on the consent form must state that confidentiality can only be broken if the participant reports immediate harm to participants or others; b) under a privacy certificate, researchers and research staff do not have to report child abuse unless the participant signs another consent form to allow child abuse reporting.
- For research conducted within the Bureau of Prisons required elements of disclosure include:

  a) identification of the researchers;

  b) anticipated uses of the results of the research;

  c) a statement that participation is completely voluntary and that the participant may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable);

  d) a statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, a researcher may not guarantee confidentiality when the participant indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the participant is an inmate, indicates intent to leave the facility without authorization;

  e) a statement that participation in the research project will have no effect on the inmate participant's release data or parole eligibility.
- For VA research: If the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective participants and about the ethical basis of the informed consent process and protocol.

14.1.1 Key Information, 2018 Requirements

For research subject to the 2018 Requirements, 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 (45 CFR 46.116(a)(5)(i)). This part of the informed consent must be organized and presented in a way that facilitates comprehension.

In general, the beginning of the informed consent form should include a concise explanation of the following:

- The fact that consent is being sought for research and that participation is voluntary;
- The purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
- The reasonably foreseeable risks or discomforts to the prospective subject;
- The benefits to the prospective subject or to others that may reasonably be expected from the research; and
- Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.

As a general matter, a brief description of these five factors would encompass the key information most likely to assist a reasonable person (or legally authorized representative) in understanding the reasons why one might or might not want to participate in research, as required by 45 CRF 46.116(a)(5)(i) and 45 CFR 46.116(a)(4).

For relatively simple research studies with limited risks or benefits, the entire consent document may be relatively brief. In such circumstances, if the 5 elements mentioned above are at the beginning of the form, followed by any additional basic or additional elements, the consent form may be deemed to satisfy 45 CFR 46.116.

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.

14.2 *Basic Elements of Informed Consent*

Informed consent must be sought from each potential subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.25.

14.2.1 Basic Elements

Informed consent must be sought from each potential subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.25.

- A statement that the **study involves research,** an explanation of the **purposes** of the research and the expected duration of the subject's participation, a description of the **procedures** to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable **risks** or discomforts to the subject;
- A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
- A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject (for biomedical research);
- A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained;
- For **applicable FDA-regulated studies** information about ClinicalTrials.gov. Applicable studies include:
    - Clinical investigations involving drugs or biologics which are controlled and other than Phase I investigations.
    - Clinical investigations involving medical devices which are prospective, controlled, and other than a small feasibility study;
- For biomedical research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury,** including who will pay for the treatment and whether other financial compensation is available;

- An explanation of whom to **contact** for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
- A statement that participation is **voluntary,** refusal to participate will involve no penalty or loss of benefits to 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;
- For research subject to the 2018 Requirements, one of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
  - 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
  - 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.
- For **FDA-regulated studies,** the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.
- An explanation of whom to contact to voice concerns or complaints about the research.
- Contact information for the COMIRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.

14.2.2 Additional Elements

One or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

- 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 (For example: appropriate when the research involves investigational test articles or other procedures in which the risks to subjects are not well known.);
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent (For example: appropriate when there are anticipated circumstances under which the investigator may terminate participation of a subject.);
- Any additional costs to the subject that may result from participation in the research (For example: appropriate when it is anticipated that subjects may have additional costs.);
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject (For example: appropriate when withdrawal from the research is associated with adverse consequences);

- 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 (For example: appropriate when the research is long term and interim information is likely to be developed during the conduct of the research.);
- The approximate number of subjects involved in the study (For example: appropriate when the research involves more than minimal risk).

For research subject to the 2018 Requirements:

- 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 (For example: appropriate when biospecimens are collected for research);
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions (For example: appropriate when the research protocol plans to return individual research results to subjects); and
- 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) (For example: appropriate when whole genome sequencing of the samples collected for the research is planned).

14.2.3 Additional Elements Required by the VA

When appropriate, VA requires one or more of the following elements of information be provided to the subject:

- Commercial Product: If applicable, that the investigator believes that the human biologic specimens obtained could be part of, or lead to the development of, commercially valuable products.
- Future Use of Specimens: if the specimens are to be retained after the end of the study for future research, where the specimens will be retained, who will have access to them, and how long they will be retained.
- Future Use of Data: If any of the data will be retained after the study for future research, where the data will be stored, and who will have access to the data.
- Re-Contact: if the subject will be re-contacted for future research whether within the VA or outside the VA.
- Payment for Participating in the Study: If appropriate, a statement regarding any payment the subject is to receive for participating in the study and how the payment is to be made.
- Disclosure of Results: If the subject will receive a report of the aggregate results or any results specific to the subject.

14.3 *Documentation of Informed Consent*

Informed consent must be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 or 21 CFR 50.27.

- Informed consent is documented by the use of a written consent form approved by the COMIRB and signed and dated by the subject or the subject's legally authorized

representative at the time of consent.
- A copy of the signed and dated consent form must be given to the person signing the form.

The consent form may be either of the following:

a. A **written consent document** that embodies the elements of informed consent. This document may be read to the subject or the subject's legally authorized representative (in the language in which it is written), but the subject or representative must be given adequate opportunity to read it themselves before it is signed. For subjects unable to read the consent form, see section 14.9;

OR

b. A **short form written consent document** (see section 14.9).

14.3.1 Documentation of the Consent Process

Consent may be documented with either a full written consent form, or using the short form procedure.

a. The full informed consent form must be signed and dated by:

1) The subject or the subject's legally authorized representative;
2) The person obtaining the informed consent;
3) A witness, if required by COMIRB (see section 14.10);

Note: The subject, or the subject's legally authorized representative, may submit the signed and dated informed consent form to the investigator or designee by facsimile or E-mail, provided an adequate, interactive consent process took place. The intention is that the IRB-approved consent process will be followed, usually involving in-person consenting; however, the IRB appreciates that there may be occasional exceptions to this process whereby an individual may need to provide consent over the phone or from long-distance. If the investigator anticipates substantial use of long-distance consenting, this should be specified in the consent process plan and approved by the IRB.

b. For documentation of consent using the short form procedure, see section 14.9.

14.4 *Waiver of Informed Consent*

The COMIRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement for informed consent provided the COMIRB finds and documents that:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration; and
- For research subject to the 2018 Requirements, 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; and
- Whenever appropriate, the subjects must be provided with additional pertinent information after participation;

Or

- 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 or service programs;
  - procedures for obtaining benefits or services under those programs;
  - possible changes in or alternatives to those programs or procedures; or
  - possible changes in methods or levels of payment for benefits or services under those programs; (Exempt Category 5) and
  - The research could not practicably be carried out without the waiver or alteration.

Note: For research regulated by the FDA, informed consent may also be waived for emergency situations (21 CFR 50.23) or for emergency research (21 CFR 50.24).

For VA regulated research only: The investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not COMIRB granted a waiver of documentation of informed consent. If COMIRB waives the requirement to maintain such a master list, COMIRB must provide written documentation in the COMIRB minutes or COMIRB protocol file justifying the waiver.

14.5 *Waiver of Documentation of Informed Consent (Waiver of Signed Consent)*

The COMIRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it determines that the research meets the criteria described below.

In cases in which the documentation requirement is waived, the COMIRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the COMIRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

14.5.1 For Studies that are NOT Regulated by the FDA

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

1. Only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality.

   Note: Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern.

   (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)

   OR
2. 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. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.

Screening, recruiting, or determining eligibility.

COMIRB 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.

For VA regulated research:

If the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing (e.g., by use of a delegation letter) to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective subjects, and about the ethical basis of the informed consent process and protocol. See VHA Directive 1200.05.

The investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not COMIRB granted a waiver of documentation of informed consent. If COMIRB waives the requirement to maintain such a master list, COMIRB must provide written documentation in the COMIRB minutes or COMIRB protocol file justifying the waiver.

COMIRB can **waive the requirement for the investigator to maintain a master list** for a given study if both of the following conditions are met:

a) There is a waiver of documentation of consent; and

b) The COMIRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality (this is always the case when the study has a certificate of confidentiality).

14.5.2 For Studies that ARE Regulated by the FDA

For studies that involve items regulated under the FDA Regulations, the COMIRB, at its discretion, may waive the requirement for the PI to obtain a signed consent document if:

- The Research presents no more than Minimal Risk of harm to the Human Subjects and involves no procedures for which written consent is normally required outside the Research context; **or**
- The requirements for an exception from informed consent for Emergency Research are met.

14.6 *Review and Approval of the Informed Consent Form*

The COMIRB is responsible for the review and approval of the informed consent form prepared by the investigator. The wording on the informed consent form must contain all of the required elements and meet all other requirements as described in this section. If the wording of the informed consent has been initially prepared by an external entity (e.g., a pharmaceutical company or a cooperative study group, including National Cancer Institute (NCI) groups) other than by a University Principal Investigator, the COMIRB needs to ensure that the wording of the consent meets all the requirements of, or has been reviewed by, the appropriate University committees and subcommittees such as the Institutional Biosafety Committee.

COMIRB approval of the wording of the consent must be documented through the use of a certification stamp on the front page that indicates the date of the most recent COMIRB approval of the document and the expiration date. If the consent form is amended during the protocol approval period, the form must have the approval date of the amendment rather than the date of the approved protocol.

For research conducted at the Eastern Colorado Health Care System, the VA Form 10-1086, Research Consent Form, must be used. COMIRB approval of the wording of the consent must be documented through the use of a certification stamp on each page that indicates the date of the most recent COMIRB approval of the document and the expiration date. The consent form must also be approved by the R&D committee indicated with the R&D committee stamp. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol. The amended consent form must also be approved by the R&D committee indicated with the R&D committee stamp.

14.7 *Consent Monitoring*

In reviewing the adequacy of informed consent procedures for proposed research, the COMIRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the panel has identified problems associated with a particular investigator or a research project.

If the panel determines that consent monitoring is required, the IRB panel will outline the request. The panel Chair and the COMIRB Director will identify the appropriate individual to monitor the consent process, and work with the individual(s) concerned to implement the plan. The consent monitoring may be conducted by Regulatory Compliance Office, panel members or another party, either affiliated or not with the institution. The PI will be notified of the panel's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. Following the monitoring, a report of the findings will be submitted to the COMIRB, which will determine the appropriate action to be taken.

14.8 *Posting of Clinical Trial Consent Forms*

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 established as a repository for such informed consent forms. It is the responsibility of the lead PI to ensure compliance with this requirement.

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. If the study team wishes to redact any information from the consent form, they should contact their program project officer. They should contact the Clinical Research Administration Office (CRAO) for review of redactions.

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.

14.9 *Assent Process*

14.9.1 Assent Process for Children

Because “assent” means a child’s affirmative agreement to participate in research, (45 CFR 46.402(b), the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the COMIRB is charged with taking into account the ages, maturity, and psychological state of the children involved. The COMIRB will review the investigators' assessment of their target population's ability to provide assent, and the general plan for assent. On an individual subject basis, it is the investigator's responsibility to ensure that each child who is capable of providing assent does so through an appropriate, COMIRB-approved assent mechanism.

The COMIRB takes into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents (generally ages 13 - 17 years) whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The COMIRB presumes that children ages 7 and older should be given an opportunity to provide assent. Written assent using a written document is usually sought.

At times there may be inconsistency between parent permission and child assent. Usually a “no” from the child overrides a “yes” from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

If the COMIRB 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 when the COMIRB determines that the subjects are capable of assenting, the COMIRB may still waive the assent requirement.

14.9.2 Assent Process for Decisionally Challenged Adults

Assent is also required by COMIRB, when it is feasible, for adults who have been determined to be unable to consent.

The assent procedure should reflect a reasonable effort to enable the person to understand, to the degree they are capable, what their participation in research will be. It is prohibited for potential subjects to be forced or coerced to participate in a research study. The assent template should be adapted as needed.

If the COMIRB determines that the capability of some or all of the decisionally challenged adults 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 individual and is available only in the context of the research, the panel may determine that assent of the individual may not be a necessary condition for proceeding with the research.

14.9.3 The Assent Form

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's / decisionally challenged adult experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. COMIRB provides an assent template as a tool for the Principal Investigator. The assent form should:

- Tell why the research is being conducted;
- Describe what will happen and for how long or how often;
- Say it's up to the child/decisionally challenged adult to participate and that it's okay to say no;
- Explain if it will hurt and if so for how long and how often;
- Say what the child's / decisionally challenged adult's other choices are;
- Describe any good things that might happen;
- Say whether there is any compensation for participating; **and**
- Ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language. COMIRB may also determine that it is appropriate for some adolescents to sign the consent document.

14.9.4 Waiver of Assent

The regulations at 45 CFR 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children's assent is appropriate:

- If the capability of some or all of the children is so limited that they cannot reasonably be consulted;
- If the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.
- If the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

14.9.5 Parental Override of a child's decision:

For studies that do not provide any prospect of direct benefit for the child, COMIRB will not approve parental override. For studies with potential benefit to the child, COMIRB will assess the child's psychological state. There comes a time in a child's illness when their autonomy and right to justice has to be respected. Such a decision by COMIRB will normally be made after consultation with the PI.

14.9.6 Surrogate Consent

This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have impaired decision-making capacity.

Unless waived by the COMIRB, informed consent must be obtained directly from the individual subject. Under appropriate conditions, investigators also may obtain informed consent from a legally authorized representative of a subject (surrogate consent).

Definition: 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 [45 CFR 46.102(c)].

The General Counsel of the University has determined that, in Colorado, the following meet the definition legally authorized representative and, thus, can give surrogate consent:

- A court appointed guardian of the person.
- A health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC) that specifies that the individual also has the power to make decisions of entry into research.
- Proxy consent under certain conditions [see section 18.5]

Investigators should consult with the General Counsel of the University when conducting research outside of Colorado to determine what the requirements for a legally authorized representative in the jurisdiction in which the research is taking place.

Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements:

The practitioner or qualified study staff may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

At the VA MEDICAL CENTER (VAMC), surrogate consent may be obtained from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care), legal guardian or special guardian, next of kin (a close relative 18 years of age or older, in the following priority: spouse, child, parent, sibiling, grandparent, or grandchild), or close friend.

If feasible, the investigator must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

14.10 *Consent and Language Barriers*

Individuals should not be denied the opportunity to participate in research solely due to an inability to read or write, or to understand English. Appropriate justification to exclude non-English-speaking, or non-reading individuals, if provided by the PI, will be considered during review of a protocol. Without such justification, studies must be prepared with a plan to enroll these individuals, as documented in section L of the Application for Protocol Review.

14.10.1 Non-reading Subjects

Sometimes a subject understands English but does not read or write, such as a subject who is legally blind or illiterate. Such subjects can understand the consent process, but are unable to adequately document consent because they cannot independently verify the consent document reflects the consent process presented to them. Therefore, there must be a witness to the consent process and documentation (see section 14.10.1).

14.10.2 Non-English-speaking Subjects

If the investigators anticipate a significant number of non-English-speaking potential subjects, they should prepare both English language and translated consent forms. After the English version is approved, a translated consent form should be obtained by the PI and submitted to COMIRB. The credentials of the translator must be provided to the IRB.

If the investigators do not anticipate a significant number of Non-English speaking subjects to be enrolled during the course of the study, they may indicate that such subjects encountered unexpectedly will be enrolled through the short form process. In these cases, researchers may rely on an oral translation of the English language consent form, along with the COMIRB template short consent form, but should take extra care in the informed consent process to ensure that the subject has understood the project. A statement in the research records (and on the English language consent form) should indicate that the translation took place, identify the translator, and document the translator's belief that the subject understands the study and the consent process. If the subject is a patient, a note about the translation should be made in the patient's research records as well. Researchers should try to provide a written translation of the vital emergency contact information.

A study is permitted to utilize the short form up to three times in the same language. If a 4th subject is to be enrolled then a translation of the entire consent form should be provided to COMIRB for approval.
The process for enrolling a non-English-speaking subject via the short form process is as follows:

1) A short form written consent document detailing the elements of informed consent is presented / translated orally to the subject or the subject's legally authorized representative. Pre-translated short forms are available in multiple languages on the COMIRB website.
2) There must be a witness (independent of the study team; see section 14.10.1) to the oral presentation; **and**
3) The COMIRB must approve a written summary (usually the full consent form) of what is presented orally to the subject or representative; **and**
4) The witness must sign both the short form and a copy of the summary; **and**
5) The person actually obtaining consent must sign a copy of the summary; **and**
6) The subject or representative must sign the short form consent document; **and**

7) A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.
8) If HIPAA authorization is required, a translated version of the HIPPA B form must be signed by the subject or the subject's legally authorized representative. Pre-translated HIPAA B forms are available in multiple languages on the COMIRB website. The HIPAA form must have been verbally presented to the subject using a translator, and the witness must also sign the form (next to subject's signature) to verify the translation adequately reflects the English form.

Additionally, any future IRB approved amendments determined to meet the requirement for re-consenting should re-consent subjects following the same process as outlined above.

Minorities, including Limited English Proficiency (LEP) persons, should be included in clinical research unless there is a clear and compelling rationale to justify why not. Any such request shall be reviewed by the IRB to determine if, in the context of the specific protocol, the inclusion of minorities, including LEP persons, is not appropriate based on:

- Respect to the health of the subjects, or
- The scientific purpose of the research, or
- The scientific design of the research.

“Lack of resources” will not be accepted as a rationale for excluding non-English-speaking subjects for any study.

14.11 *Witnesses to Subject Consent*

There are times when there must be a witness to the consent process, the documentation of consent, or both. Witnesses for any of the following situations must be impartial and independent of the study team. Such independent witnesses may include a family member of the subject, a hospital staff member who is not part of the study team, or a translator used for the consent process. This process must also be managed in accordance with the affiliate institution’s policy.

14.11.1 Subjects Unable to Read or Understand English

If a subject is provided with a full English consent form, and is unable to read or understand that consent form, there must be a witness to the consent process and documentation of consent. The role of the witness in this situation is to verify that the oral consent process took place in the subject’s preferred language.

Examples where a witness to the consent process/documentation is required:

- Non-reading (blind or illiterate) subjects
- Non-English speaking subjects consented using the Short Form (uses English summary)

Examples where a witness to the consent process/documentation is not required:

- Non-English speaking subjects, capable of reading, consented using a fully translated consent form by a speaker fluent in the subject's language
- Non-English speaking subjects, capable of reading, consented using a fully translated consent form via a translator (the PI is encouraged in this case to have the translator sign as a witness)

14.11.2 Subjects Unable to Sign a Consent Form Due to Physical Impairment

If a subject is able to read and understand English, is competent to make decisions, but is unable to sign the consent form due to physical impairment, the subject can be enrolled into the study if s/he is able to indicate approval or disapproval by other means. In this case, the investigator must document in the study records how communication with the prospective subject occurred and the specific means by which the subject communicated agreement to participate. There must be a witness to the consent process and the subject's agreement to enter the study.

14.11.3 Witness to Subject Signature

COMIRB can require a witness to the specific act of the subject signing the consent form. COMIRB may require a witness if the study involves an invasive intervention or an investigational drug or device. In this case, the witness is serving as a witness to the consent documentation only – that this particular subject signed the informed consent document for that study.

14.11.4 E-Consent (electronic informed consent)

Electronic informed consent (eIC) refers to using electronic systems and processes that may employ multiple electronic media (e.g., text, graphics, audio, video, podcasts and interactive Web sites, biological recognition devices and card readers) to convey information related to the study and to obtain and document informed consent. COMIRB will follow FDA guidance on electronic consent, which include:

a. all elements of informed consent required by FDA regulations (§ 50.25)

b. The information presented is in a language understandable to the subject or the subject’s LAR (§ 50.20)

c. All abbreviations should be spelled out at the time of first use.

d. If the eIC programs are interactive, they should be easy to navigate, allowing the user to proceed forward and backward within the system or stop and continue at a later time.

e. eIC process should be appropriate for subjects that may have difficulty navigating or using electronic systems because of lack of familiarity, poor eye sight, or impaired motor skills.

f. The eIC must be presented in a manner that minimizes the possibility of coercion or undue influence regarding the subject’s decision to participate in a study (§ 50.20).

14.12 *Withdrawal of Subject Consent*

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. It must be clear to subjects what was considered study-related intervention and what is continued follow-up. The researcher must obtain the participant’s consent for this limited participation if such an option was not clearly delineated in the original consent and COMIRB must prospectively approve the consent form. If a participant withdraws and does not want to continue follow-up the researcher cannot access records for purposes related to the study. However, the research may review study data prior to the participant’s withdrawal and may consult public records such as those establishing survival status.

15 Continuing Review of Active Protocols

Research reviewed under 2018 regulations, 45 CFR 46.109(f), and which does not require continuing review may not be assigned an expiration date. In that case the COMIRB approval letter will document that review took place under the 2018 requirements, and no continuing review will be initially required. Oversight of the research is maintained as follows:

- Annual Reminders: For studies that do not require continuing review, COMIRB sends annual notices to PIs and Primary Contacts to remind them of their ongoing responsibilities for the conduct of the research. These responsibilities include, but are not limited to, the requirement to carry out the protocols as approved, the requirement to obtain prior IRB approval for changes to the approved research except for those required to eliminate apparent immediate hazards to subjects, and the requirement to report unanticipated problems and apparent serious or continuing noncompliance, the requirement to submit annual financial interest disclosures, and to keep training up-to-date. These reminders are sent 45 days prior to the anniversary of the last IRB approval. Response to these reminders is not required unless the study is closed. The notices are sent annually until COMIRB has been notified of study closure.
- All active research is subject to routine monitoring and for cause audits.
- Continuing review may subsequently be required for issues such as an amendment that increases risk or as a corrective action due to reports of unanticipated problems or noncompliance.

For research which requires continuing review, as an assistance to investigators, COMIRB office staff will send out renewal notices to investigators 60 days and 45 days in advance of the expiration date. For research which does not require continuing review, COMIRB office staff will send out an annual reminder to investigators to remind them of their ongoing responsibilities for conducting research.

When continuing review is conducted, the following policies will be followed.

COMIRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur even when the remaining research activities are limited to the analysis of private identifiable information.

A COMIRB determination of the approval period and the need for additional supervision and/or participation is made by the COMIRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the COMIRB due to regulatory concerns, an on-site review by a subcommittee of the COMIRB might occur or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

For each initial or continuing approval, the COMIRB will indicate an approval period with an approval expiration date specified. COMIRB approval is considered to have lapsed one second after 23:59:59 of the expiration date listed.

For a study approved by the convened panel, the approval period starts on the date that the panel conducts its final review of the study; that is, the date that the convened panel approved the research or the date the convened panel approved with minor modifications (for non-substantive issues). For example, if the protocol was reviewed on April 1, 2008 at full board

but received minor modifications which were approved by the panel Chair on May 1, 2008, the expiration date will be March 31, 2009.

For a study approved under expedited review, the approval period begins on the date the COMIRB Chair or COMIRB panel member(s) designated by the Chair gives final approval to the protocol for a maximum period of one year. For example, if the protocol was reviewed on April 1, 2008 by the expedited reviewer but received minor modifications which were approved by the panel Chair on May 1, 2008, the expiration date will be April 30, 2009.

The approval date and approval expiration date are clearly noted on all COMIRB certifications sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of COMIRB approval. Therefore, continuing review and re-approval of research must occur by 23:59:59 of the listed expiration date to avoid study expiration.

15.1 *Full-Board Review at Continuing Review*

It is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

For continuing review, each panel member receives and reviews the following documentation:

- the currently approved protocol application;
- the currently approved research protocol;
- currently approved consent/ parental permission/assent form(s);
- the protocol continuing review form;
- summary of amendments since last continuing review;
- summary of reported unanticipated problems since last continuing review;
- other adverse events, untoward events or outcomes experienced by subjects reported in summary or table form since last continuing review;
- summary of gender and demographic status of subjects enrolled to-date;
- number of subjects considered as members of specific vulnerable population enrolled to-date
- any relevant recent literature
- any relevant multi-center trial reports
- if lead site, IRB approvals from other sites.
- the HIPAA Authorization forms; [If applicable]
- For VA research only: An indication from the PI (on the continuing review form) certifying that all subjects entered onto the master list of subjects for the study signed an informed consent form prior to undergoing any treatment interactions or interventions, unless the COMIRB has granted a waiver of informed consent or a waiver of the signed informed consent form. This statement is considered signed by the PI submitting the continuing review through the eRA system, or by attesting to the continuing review submission (see section 25.2.3).
- Note that any amendment to currently-approved documents will be reviewed as a separate amendment submission, which may be reviewed concurrently with a

continuing review.

In conducting continuing review of research not eligible for expedited review, all panel members are provided and review all of the above material. For continuing review of research by a convened IRB panel, the primary reviewer receives and reviews in depth the documents listed above. At the meeting, the Primary Reviewers leads the panel through the completion of the regulatory criteria for approval in the “Continuing review addendum checklist” and any other checklists appropriate to the study.

COMIRB staff attends the convened meetings and will retrieve any additional related materials the panel members request.

In the case of expedited review, the panel members may request the COMIRB office staff provide them with any additional materials required for the review.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the COMIRB, but informed consent documents must also be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

15.2 *Expedited Review at Continuing Review*

In conducting continuing review under expedited review, the reviewers receive all of the above material. The reviewer(s) complete the Continuing Review Addendum Checklist and/or the Primary Review Checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364- 60367 (see Expedited Review Categories). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review. If so, the investigator may be granted additional time to resubmit a full board application to COMIRB before the application is withdrawn but the approval still lapses and the study expires.

15.3 *What Occurs if there is a Lapse in Continuing Review*

The COMIRB and investigators must plan ahead to meet required continuing review dates. If the COMIRB has not reviewed and approved a research study by the end of the approval period specified by the COMIRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, data collection, and data analysis, unless the COMIRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for COMIRB review before the expiration date.

It is the investigator’s responsibility to initiate a renewal application, allowing sufficient time for the review and re-approval process to be completed before the current approval expires. Retrospective approval for work done after the expiration date cannot be granted.

An expiration letter (or email) will be sent to investigators at the end of the approval period.

The continuation of research after expiration of COMIRB approval is a violation of the regulations. If the COMIRB has not reviewed and approved a research study by the study’s

current expiration date, i.e., IRB approval has expired, research activities should stop. No new subjects may be enrolled in the study.

Failure to submit continuing review information on time is noncompliance and will be handled according to the noncompliance policy.

If the investigator is actively pursuing renewal with the COMIRB and the COMIRB believes that an over-riding safety concern or ethical concern is involved, a request to continue current research subjects can be made BUT enrollment of new subjects is not permitted.

- All requests from investigators to continue current subjects in research procedures must be submitted in writing to the COMIRB Director. The COMIRB Director in consultation with the panel Chair determines which subjects, if any, may continue and what procedures may be performed because stopping those research procedures will harm them. The COMIRB Director provides a written response listing the research subjects for whom suspension of the research would cause harm.

For EASTERN COLORADO HEALTH CARE SYSTEM research: If approval expires:

1) The local research office is responsible for promptly notifying the investigator.
2) The investigator must a) stop all research activities including, but not limited to, enrollment of new subjects; continuation of research interventions or interactions with currently participating subjects; and data analysis; b) Immediately submit to the Research Office and IRB Chair a list of research subjects who could be harmed by stopping study procedures; c) Immediately submit to the IRB Chair information outlining the type of research interventions being performed on subjects currently enrolled that would be harmful if stopped.
3) The Research Office will forward the list of research subjects to the Chief of Staff;
4) The IRB Chair, with appropriate consultation with the Chief of Staff, will determine within two business days whether subjects on the list may continue participating in the research interventions or interactions. If the study is FDA-regulated, the COMIRB Director and panel Chair must follow FDA requirements in 21 CFR 56.108(b) (3) in making their decision.
5) The sponsoring agency, private sponsor, the Affiliate(s), the VA Office of Research and Development (ORD), the regional VA Office of Research Oversight (ORO), or other Federal agencies must be informed, as appropriate.
6) Once the study approval has expired, COMIRB re-review and re-approval must occur before the study can resume. The COMIRB cannot retrospectively grant approval to cover a period of lapsed IRB approval.

16 Modification of an Approved Protocol

16.1 *Material Submitted*

Investigators must submit documentation to inform the COMIRB about the changes in the status of the study:

- Completed Change form;
- Revised Investigator's protocol application and/or sponsor's protocol (if applicable)
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study

- Biosafety or Radiation Safety Committee approval (Required for VA regulated research if applicable)
- Any other relevant documents provided by the investigator

Note for DoD regulated research: substantive scientific amendments to approved research shall undergo scientific review by the CU Anschutz Scientific Advisory Review Committee or similar peer review process and the review is considered by the IRB. Upload evidence of this approval with submission of the amendment.

16.2 *Expedited Review of Protocol Modifications*

COMIRB may use expedited review procedures to review "minor modifications" (see Section 12.8.2) and for minor changes to ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the panel Chair and/or designee(s) among the panel members.

The reviewer(s) receives and reviews all modified documents listed above to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications meets the regulatory criteria for approval. The reviewer uses the modifications checklist (CF-123) to determine if the modifications meet the criteria outlined in "Chair Instructions for Change Classification" to determine whether:

- The regulatory criteria for approval are met when the modification affects one or more regulatory criteria (see definition of a "minor change" in Section 11.1.3).
- Any significant new findings that arose from the review process and that might have related to subjects' willingness to continue participation were provided to subjects.
- If there is a change in investigator, the reviewer must determine that the investigator(s) has the appropriate background and experience to conduct the study.

When COMIRB is functioning as reviewing IRB on behalf of a relying site, the addition of a new relying site to the approved research generally meets the definition of a "minor change." If the addition of the site requires significant changes (see Section 11.1.3) to the research, and the research involves more than minimal risk, full board review is required.

16.3 *Full Board Review of Protocol Modifications*

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the panel must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the panel should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All panel members receive and review all modified documents provided by the investigator. When the panel reviews modifications to previously approved research, the primary reviewer uses the modifications checklist to determine whether:

- The regulatory criteria for approval are met when the modification affects one or more regulatory criteria.
- Any significant new findings that arose from the review process and that might have related to subjects' willingness to continue participation were provided to subjects.
- If there is a change in investigator, the panel must determine that the investigator(s)

has the appropriate background and experience to conduct the study.

16.4 *Administrative Review of Protocol Modifications*

Administrative changes are modifications to approved IRB records which do not change the research and do not require IRB approval. Review and acknowledgement of administrative modifications to IRB records may be conducted by COMIRB staff and may include, but are not limited to the following:

- Administrative changes or correction of typos or other errors
- Minor changes to contact information
- Verification of advertisements based on IRB approved recruitment information
- Personnel changes that involve only personnel other than key personnel
- Translations of documents into another language, when COMIRB has already approved the English version of the document, there are no changes to the approved version, and COMIRB is only verifying the credentials of the translator used.

17 Closure of Protocols

The completion or termination of the study is a change in activity and must be reported to the COMIRB. Although subjects will no longer be “at risk” under the study, a final report to the COMIRB allows it to close its files as well as providing information that may be used by the COMIRB in the evaluation and approval of related studies.

Investigators may submit a continuing review form, and a closure request letter to the COMIRB. More information may be requested depending on the status of the study.

If the study is closing prematurely, an explanation as to why this is occurring must also be submitted to COMIRB.

Study closures are reviewed as changes to approved research as described in Section 11. In most cases, study closure is reviewed under expedited procedures as a minor change to approved research. However, if closing the research involves increased risks to subjects, full board review may be required, as described in Section 11.

Also, if the study closure is associated with an unanticipated problem report, the review of the closure will be conducted in concordance with review of the unanticipated problem report as described in Section 19.

COMIRB staff may administratively close a protocol:

- With a request from the investigator when the study was never initiated or conducted,
- Without a request from the investigator for failure to respond to an expiration notice, or
- When COMIRB learns that a study ceased but COMIRB was not formally notified. Administrative closures are not suspensions or terminations of research as defined in Section 20.3.

18 Vulnerable Populations

The COMIRB determines if appropriate **additional safeguards** are in place to protect the

rights and welfare of subjects if they are likely to be members of a vulnerable population (e.g., persons who are decisionally challenged).

When some or all of the participants in a protocol are likely to be vulnerable to coercion or undue influence, the COMIRB will include additional safeguards to protect the rights and welfare of these participants. Some of the vulnerable populations that might be involved in research include children, prisoners, individuals with impaired decision making capacity, students, employees, or economically or educationally disadvantaged persons.

If the COMIRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. For example, the COMIRB will include one or more individuals who are knowledgeable about or experienced in working with children, prisoners, or individuals with impaired decision making capacity, when reviewing research that involves individuals from these populations.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional Protections for Children Involved as Subjects in Research DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts. FDA regulations also include Subpart D, which applies to all FDA-regulated research

Under University of Colorado Denver FWA00005070, the subparts apply to all research conducted at UCD. The subparts are also applied to all research conducted at the affiliate institutions.

For research subject to Environmental Protection Agency (EPA) requirements, the EPA prohibits research involving the intentional exposure or pregnant women, nursing women, or children to any substance (40 CFR Part 26.203).

For research subject to Department of Energy requirements, employees and contractors of the Department of Energy and of the National Nuclear Security Administration are considered vulnerable. If research subject to this requirement seeks to enroll these subjects, the IRB reviewer(s) will ensure the possibility of coercion and undue influence is minimized on the Primary Reviewer checklist (for example, enrolling subjects in an employer/employee relationship.)

18.1 *Panel Composition*

The Panel membership must include at least one member who is an expert in the area of the research. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

18.2 *Research Involving Children*

18.2.1 Definitions

Child – is a person who has 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.

Under Department of Education regulations - a child is a person enrolled in research who is not above the elementary or secondary education level, and who has not reached the age of majority as determined under state law.

Colorado regulations allow minors to consent for themselves for certain medical treatments.

- Age of competence is 18 years old. (CRS §13-22-101)
- An emancipated minor is a minor 15 years or older who is living separate and apart from his parent(s) or legal guardian and is managing his own financial affairs, or any minor who has contracted a lawful marriage. (CRS §13-22- 103)
- A minor parent may consent to health, medical, dental, emergency health and surgical care for his child or ward. (CRS §13-22-103).
- A minor cannot consent to donation of blood or to the penetration of the tissue for blood donation until the age of 18. (CRS §13-22-104)
- [COMIRB has interpreted, to mean donation of blood units (450 cc in one draw) and that the small, multiple volumes of blood needed for research are acceptable as long as they are less than 50cc (or 3 ml per kg) per eight week period and no more than two draws a week.]
- A minor may request birth control procedures, supplies or information. (CRS §13-22-105)
- A minor may consent for medical care and treatment for addiction to or use of drugs. (CRS §13-22-102)
- A minor may consent to exam and treatment for sexual assault but the physician must make a reasonable effort to notify the parent(s), legal guardian, or any other person having custody of such minor. (CRS § 13-22- 106)
- A minor may consent to exam and treatment for sexually transmitted diseases. (CRS §25-4-402)
- A minor may consent to an HIV/AIDS examination and treatment. The healthcare provider shall counsel the minor on the importance of bringing parents into the minor's confidence (CRS §25-4-1405)
- A minor of 15 years of age or older may consent to hospitalization for evaluation and treatment for mental health services (CRS §27-10-103)
- A pregnant minor may approve prenatal, delivery and post-delivery medical care related to the intended live birth of a child. (CRS §25-2-102)

A minor who is able to give consent (as described above) under Colorado State Law is not considered a child under federal regulations.

NOTE: It is important that investigators who conduct pediatric research understand the limitations of these regulations. COMIRB has interpreted the Colorado regulations to allow minors to consent for research procedures related to the clinical treatment which the minor has sought and can consent to under the applicable Colorado Statute without requiring parental permission. For example, if a child seeks treatment for an STD then the minor can consent to participate in STD research but the study cannot include

additional research procedures unrelated to the clinical treatment sought. Also, the minor cannot participate in genetic research as the result of seeking STD treatment.

Unless parental permission is waived, any minor parent can give permission for their child to participate in research but the parent/guardian of the minor parent must give permission for the minor parent to participate in research (if it does not fall within one of the categories above for which minors can consent as an adult).

NOTE: For research conducted in jurisdictions other than Colorado, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The General Counsel of the University's Office will provide assistance with regard to the laws in other jurisdictions.

Guardian – In Colorado, a "Guardian" of a minor means a person with the legal authority to make major decisions affecting a child including, but not limited to decisions regarding medical or surgical treatment and decisions of substantial legal significance concerning the child. There may be other individual roles, which a court appoints, that can serve as a legally-authorized representative for a child. Any individual other than a parent or legal guardian should be approved by legal counsel at the institution where the research is being conducted.

NOTE: For research conducted in jurisdictions other than Colorado, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The General Counsel of the University's Office will provide assistance with regard to the laws in other jurisdictions.

Parent - a child's biological or adoptive parent.

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

Assent - a child's affirmative agreement to participate in research. Mere failure to object, absent affirmative agreement, should not be construed as assent. The child's failure to object should not be considered assent. The assent process should be an active process.

Wards are children in the care or custody of the state, courts, or any other agency, institution or entity. *Foster Care,* under Colorado statutes, meets this Federal definition (CRS 19-1-103).

Minimal Risk means 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.

18.2.2 Allowable Categories

Research on children must be reviewed and categorized by the COMIRB into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e. **minimal risk).**
    - The panel may find that the permission of one parent is sufficient.
    - Requires assent of the child.
2. Research involving greater than minimal risk but presenting the prospect of direct

benefit to the individual subject.

- The risk is justified by the anticipated benefit to the subjects;
- The panel may find that the permission of one parent is sufficient;
- Requires assent of the child.

3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.
    - The risk represents a minor increase over minimal risk;
    - 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;
    - Permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child;
    - Requires assent of the child.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.
    - Federally-funded research in this category must be approved by the Secretary of Health and Human Services, and requires consent of either both parents, or legal guardian.
    - For non-federally-funded research, COMIRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, and law). Based on the recommendation of the panel, the COMIRB may approve the research based on either:

That the research in fact satisfies the conditions of the previous categories, as applicable;

or

The following:

- 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
- The research will be conducted in accord with sound ethical principles; and Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

18.2.3 Parental Permission

18.2.3.1 Parental Permission

In accordance with 45 CFR 46.408(b) and 21 CFR 50.55 (e), the COMIRB must determine that adequate provisions have been made for soliciting the permission of each child's parents or guardians. Permission from both parents is required for all research to be conducted with children 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; or the research falls under 1 or 2 above and the COMIRB has determined that the permission of one parent is sufficient.

Parents or guardians must be provided with the basic elements of consent as stated in 45 CFR 46.116(a) (1-8) and 21 CFR 50.25(a) (1-8) and any additional elements the IRB deems necessary.

The COMIRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 (21 CFR 50.51) or 45 CFR 46.405 (21 CFR 50.52). The COMIRB's determination of whether parental permission must be obtained from one or both parents will be documented in the Children addendum checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Parental permission from both parents is required for research to be conducted under 45 CFR 46.406 (21 CFR 50.53) and 45 CFR 46.407 (21 CFR 50.54) 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.

Under DHHS regulations, the COMIRB may waive the requirement for obtaining parental permission from a parent or legal guardian if:

- The research meets the provisions for waiver in 45 CFR 46.116(d) (1-4), OR
- The COMIRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children); **and** an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate 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.

Under FDA regulations, parental permission cannot be waived.

18.2.3.2 Assent from Children and the Assent Form

See above in section 14.8

18.2.3.3 Children who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406; 21 CFR 50.53),

only if such research is:

Related to their status as wards; **or**

Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis.*

The advocate must 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 COMIRB panel) with the research, the investigator(s), or the guardian organization.

18.2.3.4 VA Regulations: Children as Vulnerable Population in Research

VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans.

Therefore, research involving children must not be conducted by VA investigators while on official duty or at VA or approved off-site facilities unless an approval from the Medical Center Director is obtained.

If the approval is granted, the VA investigator must state the relevance of the research to the veteran population and the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.409, Additional Protections for Children Involved as Subjects in Research). NOTE: For requirements for requesting a waiver contact VA ECHCS Research Office.

For research subject to Environmental Protection Agency (EPA) requirements: The IRB will review the research according to 40 CFR 26 and 45 CFR 46 Subpart D. The IRB may only approve observational research involving children that involves greater than minimal risk but presenting the prospect of direct benefit to the individual participants if the IRB finds and documents that:

- The intervention or procedure holds out the prospect of direct benefit to the individual participant or is likely to contribute to the participant's well-being.
- The risk is justified by the anticipated benefit to the participants.
- The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 26.406.

18.3 *Research Involving Pregnant Women, Human Fetuses and Neonates*

18.3.1 Definitions

Dead fetus - a fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord.

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

Fetus - the product of conception from implantation until delivery.

Neonate means a newborn. A newborn is considered a neonate up to 30 days of age. A newborn, 31 days old will be considered a child for research purposes.

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

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

Viable, 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.

Stillborn death or **stillbirth** means death prior to the complete expulsion or extraction from its mother of a product of human conception, occurring after the twentieth week of pregnancy and does not include “induced termination of pregnancy. Colorado Revised Statutes, §25-2-102(4.5).

Induced termination of pregnancy means the purposeful interruption of a pregnancy with the intention other than producing a live-born infant or removing a dead fetus that does not result in a live birth. Colorado revised statutes, §25-2- 102(2.7).

18.3.2 Research Involving Pregnant Women or Fetuses

Research that involves pregnant women and fetuses can only occur if all of the following conditions are met (45 CFR 46.204):

When appropriate, preclinical studies (including studies on pregnant animals) and clinical studies (including studies on non-pregnant women) have been conducted and provide data for assessing the potential risks to pregnant women and fetuses;

- The risk to the fetus is caused solely by interventions or procedures that hold out the potential of direct benefit for the woman or the fetus,
  or
- If there is no potential of benefit, the risk to the fetus must be minimal, **and** the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

Any risk is the least possible for achieving the objectives of the research. No inducements, monetary or otherwise, may be offered to terminate a pregnancy.

Researchers may not take part in decisions as to the timing, method, or procedures used to terminate a pregnancy.

Members of the research team may not determine the viability of a neonate.

18.3.2.1 Who Can Consent

The **mother** may consent for the study if:

The research holds out the prospect of direct benefit to the pregnant woman, or both the pregnant woman and fetus, **or**;

If there is no benefit for the woman or fetus and the risk to the fetus is minimal, **and**;

The purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

The **mother and father** must consent for the study if:

The research holds out the prospect of direct benefit solely to the fetus.

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.

COMIRB requests that investigators document the reasons for not obtaining the father's consent in their study records.

Each individual providing consent must be fully informed regarding the reasonably foreseeable risks of the research on the fetus or neonate.

Any minor parent can give permission for their child to participate in research but the parent/guardian of the minor parent must give permission for the minor parent to participate in the research. Parental permission is not required if the minor parent is emancipated as defined by Colorado State Law.

18.3.2.2 VA Regulations

- Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.
- Research related to in vitro fertilization must not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

18.3.3 Research Involving Neonates

Neonatal research is dependent on the viability status of the neonate (45 CFR 46.205).

A neonate that is viable may participate in research only to the extent outlined by 45 CFR 46 subparts A and D.

Neonates whose viability is not certain may participate in research if COMIRB determines that:

- The research holds out the prospect of enhancing the survival of the neonate to the point of viability and the risk is minimized for achieving that goal,

Or

- The development of important biomedical knowledge which cannot be obtained by other means, and there can be no added risk to the neonate from the research.

In addition:

- The appropriate preclinical and clinical studies have been carried out that allow for adequate risk assessment.
- A neonatologist or pediatrician not associated with the research determines the

viability of the neonate.
- Informed consent of either parent of the neonate is obtained
- If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally authorized representative [LAR] of either parent may provide informed consent. COMIRB requests that you document the reasons for why you obtained the legally authorized representative's consent.
- The consent of the father is not needed if the pregnancy resulted from rape or incest.

After delivery, **nonviable neonates** may be involved in research only if the following conditions are met:

- The vital functions of the neonate are not artificially maintained
- The research will not terminate the heartbeat or respiration of the neonate
- There are no additional research risks to the neonate
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means
- Informed consent of either parent of the neonate is obtained
- The informed consent of both parents of the neonate is obtained. 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, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. Waiver and alterations of consent are not allowed, nor is the consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice.

For research subject to VA requirements: VA researchers can conduct prospective observational or retrospective record review studies that involve neonates or neonatal outcomes.

18.3.4 Neonatal Research not Otherwise Approvable

For research not funded by DHHS, if the COMIRB 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 the research is not approvable under the above provisions, then the COMIRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the COMIRB may approve the research based on either:

a. That the research in fact satisfies the conditions above, as applicable; or
b. The following:
   - 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;
   - The research will be conducted in accord with sound ethical principles; and
   - Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

DHHS-funded research that falls in this category must be approved by the Secretary of Health and Human Services. If the COMIRB 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 the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

18.3.5 Research Involving After Delivery: The Placenta, Dead Fetus or Fetal Material

Research involving the placenta following delivery; the dead fetus, macerated fetal material; or cells, tissue, or organs removed from the dead fetus shall follow the appropriate federal, state or local laws and regulations (45 CFR 46.206).

COMIRB is in compliance with the institutional policy on human fetal tissue (HFT) research. For research that is determined to be greater than minimal risk requiring full-board review or expedited minimal risk, COMIRB will conduct an ethical review based on the HFT policy. For exempt and not human subject determinations, the Scientific Ethics Committee will complete the ethics review. If a research protocol involves the procurement or release of fetal tissue from/to an external commercial or academic entity, the HFT PI attestation is required along with a draft material transfer agreement (MTA).

HFT research cannot be conducted on discarded tissue unless prospective informed consent is obtained.

No physician or institution that performs procedures for the induced termination of pregnancy shall transfer such tissue for valuable consideration to any organization or person that conducts research using fetal tissue or that transplants fetal tissue for therapeutic purposes. (Colorado revised statutes, §25-2-111.5). [***Valuable consideration*** means simply any profit or gain.

18.3.6 Research with Human Embryonic Stem Cells or Fetal Tissues

Research utilizing embryonic or fetal tissues holds promise for significant medical advances, but must be carried out in a manner that is respectful to individuals/donors, compliant with local and federal regulations, and sensitive to the community in which it is conducted. Additionally, the research must adhere to the policies and procedures of any affiliated institution in which the research is conducted. The University of Colorado Denver intends to review all projects that involve fetal tissues including human embryonic stem cells not registered listed in he NIH embryonic stem cell registry, whether or not they meet the definition of human subject research, to ensure they are conducted in accordance with the above considerations. In reviewing these projects, UC Denver relies upon the 2009 NIH guidelines on human stem cell research available at:

http://stemcells.nih.gov/policy/pages/2009guidelines.aspx

All research involving fetal tissues must be reviewed by the appropriate research committee which may include COMIRB, Institutional Animal Use and Care Committee (IACUC), Institutional Biosafety Committee (IBC), and/or the University of Colorado Denver Anschutz Medical Campus Scientific Ethics Committee (SEC). If the project meets the definition of human subject research, COMIRB review is also required in conjunction with this institutional review, per Institutional Administrative Policy regarding Conducting Human Fetal Tissue Research.

For research subject to VA requirements: Research involving the creation of a human embryo or embryos solely for research purposes or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498B of the Public Health Service Act (42 U.S.C. 289g(b)) cannot be conducted by VA Investigators, at VA facilities, or at VA approved off-site facilities.

For research subject to Environmental Protection Agency (EPA) requirements, COMIRB reviews observational research involving pregnant women and fetuses using 40 CFR 26 and 45 CFR 46 Subpart B. Observational research means any human research that does not meet the definition of research involving intentional exposure of a human subject in §26.202(a).

18.4 *Research Involving Prisoners*

Prisoners are another of the three classes that are deemed so vulnerable to exploitation in research that there are special rules protecting them. In the past, prisoners were viewed as a convenient research population. They are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, all the things that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation.

The concern that Subpart C, and this policy based on Subpart C, attempt to address is whether prisoners have any real choice in participation in research, or whether incarceration prohibits free choice.

When following Department of Justice regulations:

- Research conducted within the Bureau of Prisons must comply with 28 CFR 512, even if the research is otherwise exempt under the Common Rule. Requirements for research projects and researchers are described in 28 CFR 512.11, and include the requirements that the project must have an adequate research design and contribute to the advancement of knowledge about corrections, and that the researcher must have academic preparation or experience in the area of study of the proposed research.
- Description of physical or administrative procedures to be followed to:
    - Ensure the security of any individually identifiable data that are being collected for the study.
    - Destroy research records or remove individual identifiers from those records when the research has been completed.
- Description of any anticipated effects of the research study on organizational programs and operations.
- Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
- A statement regarding assurances and certification required by 28 CFR 46, if applicable.

18.4.1 Applicability

This policy applies to all research conducted under the auspices of UCD and its affiliates involving prisoners as subjects. Even though COMIRB may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the Colorado Department of Corrections and any other applicable State or local law. [45 CFR 46 .30 1]

18.4.2 Purpose

Because prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and not coerced decision whether or not to

participate as subjects in research, it is the purpose of this policy to provide additional safeguards for the protection of prisoners involved in research activities to which this subpart is applicable. [45 CFR 46.302] Prisoners are involved in research when they are recruited, enrolled, or undergo any research interventions while meeting the definition of a prisoner.

18.4.3 Definitions

Prisoner – 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.

The key components of this definition are 1) physical detainment of the individual, and 2) detainment as a result of a court order, either by sentencing or alternative to sentencing (e.g., probation). Specific examples include:

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners; however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.
- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
- Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
- Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise about research involving these populations.

Minimal Risk – 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.

18.4.4 Composition of the COMIRB Panel

In addition to satisfying the general requirements detailed earlier in this document, when reviewing research involving prisoners, the COMIRB must also meet the following requirements:

- A majority of the COMIRB panel (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the panel.
- At least one member of the panel must be a prisoner, or a prisoner

representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

- The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed by full board. If the prisoner representative is not present, research involving prisoners, cannot be reviewed or approved. The prisoner representative may attend the meeting by phone as long as the representative is able to participate in the meeting as if they were present in person. The prisoner representative must present their review orally to the convened meeting. When research involving prisoners is reviewed under expedited procedures, the prisoner representative must be involved in the expedited review.
- Any research involving prisoners which is eligible for expedited review (e.g., initial, continuing review or amendment, procedures detailed earlier) is reviewed by a prisoner representative, who can make all appropriate determinations.

18.4.5 Additional Duties of the COMIRB

In addition to all other responsibilities prescribed for the COMIRB in this policy document, the COMIRB will review research involving prisoners and approve such research only if it finds that:

The research falls into one of the following **permitted categories** [45 CFR 46.306]:

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

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

- Research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);

- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. [If such studies include the allocation of prisoners to a control group which may not be of direct benefit to that population then the study may proceed only after the Secretary has consulted with appropriate experts and published a notice of intent to approve in the Federal Register.]

The IRB must also determine that

- 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;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless

the principal investigator provides to the COMIRB panel justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole Board 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
- Where the panel finds there may be a need for follow-up examination or care of subjects 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 subjects of this fact.

After the IRB reviews and approves prisoner research that is supported by the DHHS, the Director or delegate on behalf of the IRB must notify OHRP and 1) provide the name and qualifications of the prisoner representative, 2) provide a reasonably detailed description of the research, 3) document the category of research under Subpart C, 4) document the additional seven protections required per 45 CFR 46.305.

Research involving prisoners may not proceed until OHRP has reviewed the IRB's determination in accordance with 45 CFR 46 Subpart C, and concurs. This requirement is detailed in the minutes of the meeting and feedback letter to the investigator. A letter informing the PI that the IRB has received concurrence from OHRP will be sent by the IRB. Only then can the PI commence the study.

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, then this occurrence must be reported to the IRB as an unanticipated problem in accordance with COMIRB policy as detailed in section 19 below. Except in the special circumstances noted below, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all of the requirements of subpart C have been satisfied with respect to the relevant protocol.

18.4.6 Safety Exception

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

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

Before terminating the enrollment of the incarcerated participant, the IRB will consider the risks associated with terminating participation in the study. If the participant cannot be terminated for health or safety reasons, the IRB will consider alternatives such as removing the participant from the study and keeping the participant on the study intervention under an alternate mechanism such as compassionate use, off label use,

etc.

18.4.7 Waiver for Epidemiology Research Involving Prisoners

The Secretary of DHHS has waived the applicability of 45 CFR 46.305a)(l) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

In which the sole purposes are:

- To describe the prevalence or incidence of a disease by identifying all cases
- To study potential risk factor associations for a disease, and
- Where the COMIRB has approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)–(7) and determined and documented that
  the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
  Prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a) (2).

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects. This research may be eligible for expedited review.

In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

18.4.8 VA Regulations Regarding Prisoners Involved in Research

Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer. If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (see 45 CFR Part 46, Subpart C 46.301 – 46.306, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects). NOTE: Requirements for requesting a waiver may be obtained by contacting the VA ECHCS Research Office.

18.5 *Persons who may be Decisionally Challenged*

Research involving subjects who are mentally ill or subjects with impaired decision-making capacity warrants special attention. Research involving these populations may present greater than minimal risk; may not offer direct medical benefit to the subject; and may include a research design that calls for washout, placebo, or symptom provocation. In addition, these

populations are considered to be vulnerable to coercion.

"Decisonally challenged" includes adult subjects who are:

- Incompetent to consent
- Cognitively Impaired
- Have impaired decisional capacity due to the environment or situation

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

Cognitively Impaired: having a psychiatric disorder (e.g. psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g. dementia, delirium) or a developmental disorder (e.g. mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

Impaired Decisional Capacity: having the ability to provide informed consent to or refusal of medical treatment but this ability is compromised by external factors. To give informed consent the subject must be given all relevant information pertinent to the decision and be able to recognize that a decision is needed, and process the information (i.e. discuss it, remember it, evaluate the various factors, and understand the consequences). This process may be compromised due to external factors such as time limitations or stress.

COMIRB recognizes that enrollment of incompetent subjects may involve varying circumstances and degrees of incompetence. For example, a subject may be considered mentally/cognitively impaired (e.g. psychiatric disorder) and have the capacity to consent to or refuse to participate in research. However, a mentally/cognitively impaired subject may lack decisional capacity, in which case consent from a legally authorized representative or proxy decision maker must be obtained.

Colorado State Law is silent on the subject of proxy decision makers for medical research; therefore, in response to the need, COMIRB has established the following policy defining those who may serve in this capacity, and under what conditions. These requirements follow Colorado Revised Statute 15-18.5-103, which define proxy decision makers for medical treatment.

The definition does not mention research. However this is a broad definition of medical treatment that presumably would cover research in which there is a prospect of benefit to the subjects. Until a court decides whether this definition of medical treatment includes medical research, the question is left open.

For research conducted at UCD and its affiliates, which requires a proxy decision-maker, the research protocol must document how the study meets the above definition of treatment. Specifically, the protocol must state how the research intervention(s) serve to maintain, diagnose, treat or provide for a patient's physical or mental health or personal care.

Types of research that would not be expected to meet the definition of medical treatment are as follows. While it is not expected that these types of research will qualify, if an investigator believes that a protocol utilizing one of the following methodologies does meet the definition, the protocol should state how specific elements of the study contribute to treatment.

Examples:

Phase 1 Clinical Trials

Gene Array Studies
Tissue Banking Studies that are for unspecified purposes
Specimen Collection for future use

For those studies in which COMIRB determines that the research could reasonably be considered to be medical treatment, the Colorado Proxy Decision–Makers for Medical Treatment Act has additional requirements. Most notably, under section 15-18.5-103(2), a court or the attending physician must make a determination that an adult patient lacks decisional capacity to provide informed consent, and it must be documented in the patient's medical record. Second, section 15-18.5-103(3) states that the "interested parties" must decide who among them will make decisions regarding the care of the patient. The "interested parties" are defined as "the patient's spouse, either parent of the patient, any adult child, sibling, or grandchild of the patient, or any close friend of the patient." The medical record must document the specific procedures that are followed in this determination of a proxy decision-maker.

18.5.1 COMIRB Panel Composition

The COMIRB membership must include at least one member who is an expert in decisional impairment or working with individuals with limited decision-making capacity. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population.

18.5.2 Approval Criteria

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

- Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
- The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.
- Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents [appointed under Durable Power of Attorney for Health Care (DPAHC)], guardians or proxy consent decision makers in accordance with Colorado State law must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.
- For research conducted under the auspices of the **VA MEDICAL CENTER (VAMC)],** authorized persons include: health care agents [appointed under

Durable Power of Attorney for Health Care (DPAHC)], or legal guardians or special guardians, next of kin - a close relative of the patient 18 years of age or older in the following priority: spouse, child, parent, sibling, grandparent or grandchild, then close friend must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

- **NOTE:** Per VHA Directive 1200.05, an individual who is qualified as a LAR to provide informed consent on behalf of a prospective research subject may **not always** qualify as a personal representative for purposes of consent to use or disclose a human subject's PHI (i.e., signing a HIPAA authorization). Therefore, in circumstances involving authorization for use or disclosure of a human subject's PHI, the investigator must ensure the LAR meets the requirements of a personal representative (legal guardian or power of attorney) in HIPAA and the Privacy Act of 1974 prior to the LAR's signing a HIPAA authorization (see VHA Directive 1605.1).

18.5.3 Additional Concerns

Both investigators and COMIRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. It is the responsibility of investigators to monitor the decision-making capacity of subjects enrolled in research studies and to determine if surrogate consent must be re-obtained.

The COMIRB will require investigators to conduct a **competency assessment** whenever there is a possibility of either impaired mental status or decision-making capacity in prospective subjects. In general, the COMIRB recommends using a method of assessment that directly evaluates an individual's ability to comprehend the proposed study and to weigh the risks and benefits of entering the study.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

18.6 Research conducted in an International Setting

18.6.1 Reviewing International Research

All human subject research protocols that involve the PI or members of the research team traveling outside the USA to recruit, consent, conduct research activities and / or collect data are required to be pre-reviewed by the International Research Advisory Committee (IRAC) prior to the normal protocol review as detailed in this document for initial full board or expedited protocols. Additionally, any research which is funded by the PI (or PI's grant), or research occurring in another country under the direction of the PI (or the PI's protocol), must be pre-reviewed by the IRAC. See COMIRB SOP CP-028.

Review by IRAC
COMIRB must be aware of local conditions and situations that may affect the design or implementation of the research. For example; local regulations governing research with minors can vary from country to country. Also local social and political conditions may

distort the way informed consent documents are viewed by foreign participants, and a request for a subject's signature may be viewed with suspicion. Offering monetary compensation or access to health care may also be coercive in certain settings.

COMIRB generally requires the involvement of a local IRB that has knowledge of the local research context. This is important because the local research environment and the characteristics of the subject being enrolled can vary greatly. The degree of local knowledge required is based in part on the degree of risk presented by the research.

Because of the detailed information needed for review, international research should be submitted on the COMIRB application form, even if it is a request for exemption.

COMIRB relies on the PI to provide a clear description of the research environment and the plan to address cultural sensitivities. This plan should be supported by external material verifying this position. COMIRB also needs to verify that the PI has the expertise and resources to conduct an international study.

All researchers conducting such research are recommended to complete the CITI course on International Research prior to approval of the protocol.

IRAC Membership:

- COMIRB Chairs
- COMIRB Expedited/Exempt reviewers
- Senior COMIRB administration
- Representation from the Office of International Affairs
- Representation from the Center for Global Health
- Representation from faculty with expertise in international research
- Representation from the Export Control Office
- Ad hoc members: Experts with working knowledge of the local sites at the request of the committee.

IRAC Procedures:

The IRAC will review the protocol, Application with attachment B, and the consent form(s) to ensure that the study is culturally appropriate to be conducted in at the locations requested. IRAC may request additional documents if deemed necessary to evaluate the adequacy of the international study.

The committee in conjunction with the expert(s) and based on conversation with the PI and mentor/advisor (if applicable) complete the IRAC checklist (CF-112).

The committee can make the following recommendations:

- Acceptable as submitted
- Acceptable with the condition of subsequent approval by a local IRB/EC before the research begins
- Requires changes and to be re-evaluated by this committee prior to IRB review

The IRAC must confirm in collaboration with the PI (by completing Attachment B), regional experts and legal counsel:

- To ensure that local laws are followed;
- Confirm the researchers and research staff has the appropriate qualifications from conducting research in that country;

- Ensure that there is appropriate post-approval monitoring;
- Ensure that there is an appropriate mechanism for handling complaints, noncompliance and unanticipated problems involving risk to subjects or others.

The IRAC documents its findings using the IRAC checklist. A copy of the committee's recommendations will be sent to the PI and /or mentor/advisor if changes to the protocol are requested. The IRB panel or reviewer will have access to review the checklist, minutes and feedback letter from the IRAC review as part of their IRB review.

There are additional safeguards for research conducted with all international populations, including DoD-funded research. COMIRB will verify the following:

1. The researcher has permission to conduct research in that country by certification, or local ethics review. The COMIRB IRAC will request the local IRB or ethics approval and the study will not be approved to begin recruitment until a copy has been obtained by COMIRB. If a local ethics review will not be performed, will request input from an ad-hoc member or consultant (see 5.2.3) with working knowledge of the local site, or from a respected local resource such as a local tribal elder or local partner organization.

2. The researcher follows all local laws, regulations, customs, and practices. IRAC membership is made up of UCD faculty with expertise in conducting research internationally and the IRAC reviewers will ensure that all local laws, regulations, customs and practices are followed prior to moving forward for a board and/or Chair review in collaboration with the local ethics board. The IRAC team may also consult with university legal counsel as needed.

18.6.2 Monitoring approved international research

COMIRB relies on the PI to assure reliable access to collaborating investigators in the field. Unanticipated problem reporting must also still be made in a timely manner. Any problems encountered by the foreign investigator or the research team in the field should be reported to the study sponsor, relevant regulatory agencies and COMIRB.

18.6.3 For VA regulated international research

All participants who participate as subjects in research at international sites must be provided appropriate protections that are in accord with those given to research subjects within the U.S. as well as protections considered appropriate by local authority and custom at the international site.

VHA policy states that approval must be obtained from the Facility Director prior to initiating any international research that meets the following definition:

For the purpose of VA policy, International Research is defined as any VA-approved human subjects research conducted at international sites (not within the U.S., its territories, or Commonwealths) or to VA-approved research using either human biological specimens or human data originating from an international site whether identified, de-identified or coded. If the research meets the definition of human subject research, the research also needs to be reviewed and approved by COMIRB. This policy applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, Memoranda of Understanding (MOU), Cooperative Research and Development Agreements (CRADA), grants, or contracts. Also, All VA-approved research must be approved by the Research

and Development (R&D) Committee.

Multi-site trials are only covered under this definition if:

1. VA is the sponsor
2. VA functions as the coordinating center
3. VA subcontracts to a foreign site
4. The principal investigator (PI) for the total project is a VA investigator.

This Directive does not apply if VA is only one of the participating sites and the trial does not meet the preceding conditions. *(VHA Directive 2005-050)*

18.6.4 For DoD-funded or -conducted international research

DoD-funded or -conducted research involving human subjects who are not U.S. citizens or DoD personnel, conducted outside the United States (and its territories and possessions) requires permission of the host country. Investigators are responsible for ensuring that such permission has been obtained.

IRAC and COMIRB will confirm that all applicable national laws and requirements of the foreign country have been met. IRAC and COMIRB shall also consider the cultural sensitivities in the setting where the research will take place.

Approval by the appropriate DoD component's Human Research Protection Official (HRPO) is required prior to research starting when human subjects research is conducted in a foreign country, unless conducted by a DoD overseas institution, or if the research only involves DoD-affiliated personnel who are US citizens. Investigators are responsible for obtaining HRPO approval after IRB approval. Documentation of HRPO approval must be submitted to COMIRB as soon as possible after it is obtained, and by no later than the first Continuing Review.

19 Unanticipated Problems Involving Risks to Subject or Others and Adverse Events

19.1 *Definitions*

Unanticipated Problem Involving Risks to Participants or Others (Unanticipated Problem): Any event or information that was unforeseen and indicates that the research procedures, approved by the IRB and carried out as expected, caused harm (including physical, psychological, economic, or social harm) to participants or others, or indicates that participants or others are at increased risk of harm than was previously known or recognized.

Adverse Event: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite).

Unanticipated event: Any adverse experience where the nature, severity or frequency is not identified in the investigational brochure described in the application form or detailed in the consent form. This can also include noncompliance issues such as over enrollment of subjects without prior COMIRB approval.

Possibly related: In the opinion of the PI, the adverse event is unlikely to be related to the study intervention, drug or device.

Probably related: In the opinion of the PI, it is more likely than not that the adverse event is related to the study intervention, drug or device.

Definitely related: In the opinion of the PI, it is very likely that the adverse event is related to the study intervention, drug or device.

Related to the research: An event is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not [probably] to be caused by the research procedures or if it is more likely that not [probably] that the event affects the rights and welfare of current participants.

Internal event / problem: An occurrence involving research subjects enrolled in a project approved by COMIRB and directed by a principal investigator employed by the University of Colorado Denver (or affiliate site) or one whose project is under the purview of the COMIRB).

External event / problem: An occurrence involving research subjects enrolled in multi-center research projects that do not fall under the purview of the COMIRB (i.e. sites other than UCD, UCH, VAMC, and Denver Health).

Prompt Reporting: Reportable events must be submitted to COMIRB within 5 working days of the event or knowledge of the event.

For VA research only, the following definitions outlined in VHA Directive 1058.01 apply:

An unanticipated problem involving risks to participants or others (UPIRTSO) in human participants research is an incident, experience, or outcome that is: unexpected; related or possibly related to participation in the research; and indicative of the research placing participants or others at substantively greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (VHA Directive 1058.01 Section 3)

The term "unexpected" refers to an incident, experience, or outcome that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

The phrase "related to participation in the research" means a logical sequence of cause and effect shows that the study procedures were the reason for the incident, experience, or outcome.

The phrase "possibly related to participation in the research" implies a lesser degree of certainty about causality and refers to an incident, experience, or outcome for which there is some evidence to reasonably suggest a causal relationship between study procedures and the incident, experience, or outcome.

19.2 *Reportable Events*

Investigators must report the following to COMIRB within 5 days:

- An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, psychological events, drug errors, hospitalizations, or death).
- Adverse events which in the opinion of the principal investigator are both unexpected and probably or definitely related to the intervention/ drug or device.
- An unforeseen development that potentially increases the likelihood of harm to participants or others in the future.
- Information that indicates a change to the risks or potential benefits of the research.

For example:

- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the COMIRB.
- A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the COMIRB.
- A problem involving data collection, data storage, privacy or confidentiality.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Pregnancy of a participant or spouse in a protocol that specifically exclude pregnancy due to the potential risks of the intervention or treatment on the fetus.
- Change to the protocol taken without prior COMIRB review to eliminate an apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional change to the COMIRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- Study related event that requires prompt reporting to the sponsor, if it meets the above definition of an unanticipated problem.
- Sponsor imposed suspension for risk.
- Noncompliance by the PI or research team
- Any other problem that caused a risk to the participant or others

19.3 *Reporting*

Principal investigators or their designee should report the above events using the unanticipated report form within 5 days.

The unanticipated problem form should also be used to submit the following documents to COMIRB for prompt review if they meet the criteria for an unanticipated problem:

- Medwatch reports
- IND reports
- DSMB or other safety review reports
- Investigational Brochures changes
- Changes to Package Inserts
- Audit reports
- Complaints

If the information provided in these documents does not meet the definition of an unanticipated problem as outlined above then this information should be submitted as a modification to approved documents if applicable or at continuing review, in aggregate format, as additional safety information.

At the time of continuing review, the PI should submit an aggregate summary of all adverse events occurring in the last review period that did not meet the definition of an unanticipated problem, so that COMIRB can ensure adequate safety monitoring is occurring for the study. If there is a study monitor (safety officer, DMC, or DSMB) reviewing all adverse events, COMIRB will delegate the review of these events to that monitor.

At the time of continuing review, the PI should submit an aggregate summary of all protocol violations occurring in the last review period that did not meet the above criteria for reporting to COMIRB within five days.

19.4 *COMIRB Review of Reports*

When an unanticipated problem report is submitted to the COMIRB office, it is routed to the unanticipated problem triage team that includes senior IRB staff. The senior IRB staff will immediately review the unanticipated problem report and if there is potential serious or continuing noncompliance, will notify the panel coordinators to assign to a reviewer as a priority review. The triage team will follow the VA policy on potential serious or continuing noncompliance and for unanticipated problems that meet the policy definition, panel coordinators will assign to the next full-board panel meeting.

If the COMIRB Chair or designee considers that either (1) the problem was foreseen OR (2) the problem was not related (not at least probably related) to the research design or procedures OR (3) no participants or others were harmed AND participants or others are not at increased risk of harm, the IRB Chair or Director indicates on the unanticipated problem checklist that the problem is not an unanticipated problem. The form is filed in the protocol record, the determination is communicated to the investigator and no further action is taken.

If the unanticipated problem requires investigation because it is a complaint, or to determine if it potentially is either serious noncompliance or continued noncompliance, then it is handled according to section 20 below. A report of the sub-committee will then be submitted to the IRB to be reviewed as an unanticipated problem.

If the COMIRB Chair considers that the problem is an unanticipated problem, but that the risk is no more than minimal, the chair or designee will review:

1. The currently approved protocol
2. The currently approved COMIRB application form
3. The currently approved consent document
4. Previous reports of unanticipated problems involving risks to participants or others
5. The report of the unanticipated problem involving risks to subjects or others

After reviewing all of the materials, the chair or designee will take appropriate action depending on the nature of the risk involved, including modification of the protocol or the consent form, if applicable. The chair or designee uses the “Unanticipated problem checklist for Chairs” to record the results of the review. The results of the chair or designee’s review will be recorded in the protocol record, communicated to the investigator, reported to the COMIRB panel, and referred to the COMIRB Office to be handled according to the reporting procedures.

If the chair considers that changes to the consent form or protocol modifications are required, the convened IRB is to review the unanticipated problem involving risks to participants or others,

unless the change is a minor change. For example, the addition of new risks to the consent or a change in procedures indicates that the problem involves more than minimal risk to participants and is to be reviewed by the convened IRB. All reported unanticipated problems where the risk is more than minimal will be reviewed at a convened COMIRB panel meeting. Based on the information received from the investigator, the COMIRB Chair may suspend research to ensure protection of the rights and welfare of participants prior to review by the panel. Suspension directives made by the panel Chair or COMIRB Director must be reported to the next meeting of the convened panel and reported to the institution and federal agencies in accordance with the reporting policy detailed below.

All panel members are provided a copy of the Unanticipated Problem Form and supporting documents provided by the investigator, including:.

1. The currently approved protocol
2. The currently approved consent document
3. Previous reports of unanticipated problems involving risks to participants or others
4. The investigator's brochure, if one exists

The primary reviewer uses the "Unanticipated problem – full board reviewer checklist." If the panel considers the event to not represent an unanticipated problem, the results of the review are recorded in the protocol record, communicated to the investigator and no further action is taken.

If the panel considers the event to represent an unanticipated problem, where the risk is more than minimal, the panel will consider the following actions:

1. Modification of the protocol
2. Modification of the information disclosed during the consent process
3. Providing additional information to current participants (This must be done whenever the information may relate to the participant's willingness to continue participation)
4. Providing additional information to past participants
5. Requiring current participants to re-consent to participation
6. Alteration of the frequency of continuing review
7. Observation of the research or the consent process
8. Requiring additional training of the investigator
9. Notification of investigators at other sites
10. Termination or suspension of the research
11. Obtaining additional information

The results of the panel review are recorded in the protocol record, communicated to the investigator and referred to the COMIRB Office to be handled according to the reporting procedures described below.

20 Complaints, Noncompliance, Suspensions or Terminations of COMIRB Approval of Research

20.1 *Complaints*

The Chair of the panel and the Director of the COMIRB Office will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the COMIRB. This includes complaints, concerns, and appeals from investigators, research participants and others.

Complaints reported to COMIRB will be evaluated to determine if the complaint involves

unanticipated problems involving risks to participants or others or allegations of noncompliance. If the complaint meets the definition of noncompliance, it will be considered an allegation of noncompliance according to section 20.2. If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 19.

20.2 *Noncompliance*

All members of the research community of the participating institutions involved in human subject research are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and institutional and COMIRB policies governing the conduct of research involving human subjects.*

The Principal Investigator is responsible for reporting any noncompliance by study personnel to the COMIRB. For research subject to VHA Directive 1058.01, all VA personnel have responsibility for reporting apparent serious or continuing noncompliance.

Reports of apparent serious or continuing noncompliance must be submitted to the COMIRB Office within 5 working days of discovery of this noncompliance. The report must include a complete description of the apparent serious or continuing noncompliance, the personnel involved and a description of the noncompliance.

* **When following VA requirements**, VA policies require all VA employees (including WOC and IPA employees) to notify the IRB in writing of serious unanticipated problems involving risks to participants or others. Serious unanticipated problems involving risks to participants or others include:

- Interruptions of participant enrollments or other research activities due to concerns about the safety, rights, or welfare of human research participants, research staff, or others.
- Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death.
- Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects.
- Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted.
- The unfounded classification of a serious adverse event as "anticipated" constitutes serious noncompliance.

Noncompliance is defined as failure to comply with any of the regulations and COMIRB policies described in this document, including VHA Directive 1058.01 for VA research, and failure to follow the determinations of the COMIRB. Noncompliance may be minor or sporadic or it may be serious or continuing.

Serious Noncompliance is defined as failure to follow any of the regulations and policies or failure to follow the determinations of the COMIRB and which, in the judgment of either the COMIRB Chair(s) or the convened panel, increases risks to participants, decreases potential benefits, or compromises the integrity of the human research protection program. Research being conducted without prior IRB approval is generally considered serious noncompliance.

For research subject to VHA Directive 1058.01, Serious Noncompliance is any failure to

adhere to requirements for conducting research that may reasonably be regarded as:

(1) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of human research subjects or others, including their rights to privacy and confidentiality of identifiable private information;

(2) Presenting a genuine risk of substantive harm to the safety, rights, or welfare of research personnel who conduct research;

(3) Presenting a genuine risk of substantive harm to the health or welfare of animals used in research;

(4) Presenting a genuine risk of substantive reputational harm to VA; or

(5) Substantively compromising a VA medical facility's Human Research Protection Program (HRPP).

Continuing Noncompliance is defined as a pattern of noncompliance that, in the judgment of the panel Chair(s) or convened panel, suggests a likelihood that instances of noncompliance will continue without intervention. Continuing noncompliance also includes failure to respond to a request to resolve an episode of noncompliance within 30 days.

For research subject to VHA Directive 1058.01, Continuing Noncompliance means repeated instances of noncompliance with applicable laws, regulations, policies, agreements, or determinations of a research review committee or the prolonged persistence of noncompliance occurring after its identification, awareness, or implementation of a corrective action intended to effectively resolve the noncompliance.

Allegation of Noncompliance is defined as an unproved assertion of noncompliance.

Finding of Noncompliance is defined as an allegation of noncompliance that is proven true or a report of noncompliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator that the protocol was willfully not followed would represent reports of noncompliance that would require no further action to determine their truth and would therefore represent findings of noncompliance.)

20.2.1 Review of Allegations of Noncompliance

The COMIRB Chair(s) and Director will review the allegation and make a determination as to the truthfulness of the allegation. The initial findings of fact will be conducted in conjunction with the appropriate affiliate compliance office(s). The findings of fact may include requesting additional information from the PI, other members of the research team, interviewing subjects or an audit of the research in question.

If, in the judgment of the COMIRB Chair(s) and Director, the reported allegation of noncompliance is not true, no further action will be taken. If, in the judgment of the COMIRB Chair(s) and Director, the reported allegation of noncompliance is true, the noncompliance will be processed according to the process described below.

If, in the judgment of the COMIRB Chair(s) and Director, any allegation or findings of noncompliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the COMIRB Chair or Director may suspend the research as described below and reported to the next IRB panel (See 19.4 for IRB review process).

All allegations of noncompliance will be reviewed by the Compliance Board consisting of all COMIRB Chair(s), Exempt/expedited reviewers, the Director and senior COMIRB administration, and Associate Vice Chancellor for Regulatory Compliance (IO) unless

one of these individuals has a conflict of interest with the study or the investigator. If a conflict of interest is declared then that individual will be excluded from the investigation, discussion and determination.

The COMIRB Chair(s) and Director or Compliance Board will also make a decision about whether a preliminary determination should be reported to regulatory agencies and institutional officials in accordance with section 21 below, or whether additional information is required before making such reports. A report must be submitted within 30 days of an initial finding in fact, or a convened IRB panel's determination, of serious or continuing noncompliance. Once all the information has been collected then the review of the allegation will be made by the appropriate IRB panel.

20.2.2 Review of Findings of Noncompliance

The IRB review process is described in Section 19.4. All findings of apparent serious or continuing noncompliance referred to the Compliance Board will be reviewed at a meeting of the Compliance Board. All members will receive documentation necessary to evaluate the report.

Compliance Board may:

- Find that there is no issue of noncompliance;
- Find that there is noncompliance that is neither serious nor continuing and an adequate corrective action plan is in place;
- Find that there may be serious or continuing noncompliance; or
- Request additional information.

If in the judgment of the Compliance Board, the reported finding of noncompliance is not serious, not continuing, and the proposed corrective action plan seems adequate, no further action is required.

If the allegation of noncompliance was protocol-specific, it is reported at the next convened panel meeting of the panel responsible for that protocol. If the allegation of noncompliance relates to an investigator the issue will be reported by the appropriate Chairs to each panel that is responsible for protocols involving that investigator in accordance with section 20.2.5. If the Compliance Board requests an audit, the procedure described below will be followed. If there is concern that this issue of noncompliance may raise to research misconduct (falsification or fabrication of data or plagiarism) then the UCD Research Integrity Officer will be contacted to review the allegation in accordance with UCD policies and procedures.

20.2.3 For Cause Audit Procedures

A determination may be made by the Compliance Board that inquiry for cause is necessary based on several issues that may include but are not limited to:

- Subjects' complaint(s) that rights were violated;
- Report(s) that investigator is not following the protocol as approved by COMIRB;
- Unusual and/or unexplained adverse events in a study;
- FDA audit report of an investigator;
- Repeated failure of investigator to report required information to the COMIRB.

If the Compliance Board requests an audit, the board will issue specific areas of focus to the Quality Assurance (QA) Team, unless a routine audit is requested. The QA Team will conduct the audit in accordance with their policies and procedures. If the issue

involves activity at one of the affiliate hospitals then the compliance officer at the affiliate hospital may be asked to conduct the audit or assist the QA Teram with the audit. The results of the for cause or compliance audit will be reviewed at a Compliance Board meeting where the board will receive a report from the subcommittee.

20.2.4 Final Review by Compliance Board

The compliance board may take one or more of the following actions:

- Request for additional information;
- Acceptance of the proposed corrective action plan;
- Modifications to the proposed corrective action plan;
- Broadening of the investigation
- Request a correction action plan from the investigator;
- Recommend to the responsible panels whether the noncompliance should be considered serious or continuing

20.2.5 Final Review by convened IRB panel(s)

If there is no assigned COMIRB panel for a protocol (e.g., the protocol is under the oversight of an external IRB), the recommendation of the Compliance Board review will be communicated to the IRB of Record and /or to the IO.

The COMIRB compliance staff person will ensure that the results of the audit and/or report and/or recommendations of the Compliance Board will be reviewed at the appropriate convened IRB panel(s). All IRB members will be provided with a copy of the report, the original audit report, result of any investigation, and recommendations of the Compliance Board. If the noncompliance involves a specific protocol, a copy of the protocol and consent document may also be provided to all IRB members (as needed). If the results of the inquiry or the report from the Compliance Board substantiates the finding of serious or continuing noncompliance and the IRB panel concurs, the IRB panel's possible actions could include, but are not limited to:

- Request a corrective action plan from the investigator;
- Verification that participant selection is appropriate and observation of the actual informed consent;
- An increase in data and safety monitoring of the research activity;
- Request a directed audit of targeted areas of concern;
- Request a status report after each participant receives intervention;
- Modify the continuing review cycle;
- Request additional Investigator and staff education;
- Notify current subjects, if the information about the noncompliance might affect their willingness to continue participation;
- Modification of the protocol;
- Modification of the information disclosed during the consent process;
- Requiring current participants to re-consent to participation;
- Suspend the study (See below); or
- Terminate the study (See below)

The investigator is informed of the COMIRB determination and the basis for the determination in writing and is given a chance to respond. If the panel determines that

the noncompliance was serious or continuing or if an initial report had been sent to regulatory agencies and institutional officials, the results of the final review will be reported according to COMIRB policy outlined in section 21.

For research subject to VHA Directive 1058.01:

The IRB will review the written notification of apparent serious or continuing noncompliance at its next convened meeting, not to exceed 30 calendar days after the date of written notification. If immediate attention is required, an IRB meeting will be convened. The IRB chair may take interim action to eliminate apparent immediate hazards to participants.

The IRB will determine and document within 60 calendar days of the convened IRB's initial review: whether or not serious or continuing noncompliance actually occurred; and if so, what, if any, remedial actions are needed to resolve present noncompliance or prevent future noncompliance.

20.3 *Suspension or Termination*

Suspension of COMIRB approval is a directive of the convened panel or panel Chair or COMIRB Director either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of COMIRB approval is a directive of the convened panel to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The panel Chair or COMIRB Director may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the panel Chair or COMIRB Director must be reported to a meeting of the convened appropriate panel.

When study approval is suspended by the convened panel or individual ordering the suspension, in addition to stopping further enrollment on the study, the convened panel or individual ordering the suspension will determine what, if any, research activities can continue, determine if subjects currently participating should be notified that the study has been suspended. The convened panel or individual ordering the suspension will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened panel or individual ordering the suspension, the convened panel or individual ordering the suspension will require that the subjects should be so informed and that any adverse events/outcomes be reported to the panel and the sponsor.

Research may only be terminated by the convened panel. Terminations of protocols approved under expedited review must still be made by the convened panel.

When study approval is terminated by the convened panel, in addition to stopping all research activities, the convened panel ordering the termination will notify any subjects currently participating that the study has been terminated. The convened panel ordering termination will review and approve a plan for withdrawal of any enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research.

21 Reporting to Regulatory Agencies and Institutional Officials

The COMIRB office will initiate these procedures as soon as the COMIRB takes any of the following actions:

- Determines that an event is considered an unanticipated problem involving risks to participants or others
- Determines that noncompliance was serious or continuing
- Determines a preliminary report should be made when initiating an audit to determine if noncompliance was serious or continuing
- Suspends or terminates approval of research

The Director or designee prepares a letter that contains the following information:

a) The nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing noncompliance, suspension or termination of approval of research)
b) Name of the institution conducting the research
c) Title of the research project and/or grant proposal in which the problem occurred
d) Name of the principal investigator on the protocol
e) Number of the research project assigned by the COMIRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
f) A detailed description of the problem including the findings of the organization and the reasons for the COMIRB's decision
g) Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)
h) Plans, if any, to send a follow-up or final report by the earlier of the following options:
   1) a specific date or
   2) when an investigation has been completed or a corrective action plan has been implemented

The COMIRB Chair(s) and the AVC for Regulatory Compliance review the letter and modify the letter as needed. The Institutional Official reviews and signs the letter and returns it to the Director, COMIRB to distribute.

The AVC for Regulatory Compliance or designee sends a copy of the report to:

a) The IRB panel(s) impacted by including the letter in the next agenda packet as an information item
b) The Institutional Official
c) OHRP, if the research is subject to DHHS or FDA regulations, or subject to a DHHS federal wide assurance
d) FDA, if the study is subject to FDA regulations.
e) CEO of each of the Affiliate(s).
f) For EASTERN COLORADO HEALTH CARE SYSTEM research, the report is sent to the Denver VAMC Research Office, to be forwarded to:
   i) The Chair of the EASTERN COLORADO HEALTH CARE SYSTEM Research and Development Committee
   ii) The VA Research Office
   iii) The Regional VA Office of Research Oversight

For research subject to VHA Directive 1058.01:

Additionally, for VA research all **adverse events** that are determined to meet the definition of unanticipated problem and therefore reportable, the IRB must report the event to the VA facility Director as soon as possible, but no later than 5 business days after the determination. The VA facility Director will then report the event to ORO within an additional 5 business days.

If the IRB determines that serious or continuing noncompliance actually occurred, it must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing of its determinations under within five (5) business days after making those determinations.

For privacy and confidentiality breaches including any unauthorized use, loss or disclosure of individually-identifiable subject data, the Denver VA privacy officer must be informed.

For IT security breaches including violations of VA information security, the Denver VA Information Security Officer (ISO) must be informed.

g) If the study is conducted or funded by any Federal Agency other than DHHS that is subject to "The Common Rule," the report is sent to OHRP and/or the head of the agency or defined contact as required by the agency such as DoD (i.e.,, HRPO) or DoE.
   Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, or the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.
h) Principal investigator
i) Office of Grants and Contracts to report to the appropriate funding agency
j) Clinical Research Administration to report to the Sponsor, if the study is sponsored
k) Contract research organization, if the study is overseen by a contract research organization
l) Chairman or supervisor of the principal investigator
m) Research Quality Assurance and Education Program Director
n) The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity
o) The Information Security Officer of an organization if the event involved violations of information security requirements of that organization
p) Office of Risk Management
q) Others as deemed appropriate by the Institutional Official

For research supported by the Department of Defense (DoD):

Any unanticipated problems involving risks to participants or others, serious or continuing noncompliance, and any suspension or termination of research, must be promptly (no longer than within 30 days) reported to the DoD human research protection officer.

For research subject to Department of Energy requirements:

The Human Subjects Protection (HSP) Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager) must be notified by the researcher of the following:

Within 48 hours:

- Any significant adverse events, unanticipated problems, and complaints

about the research, with a description of any corrective actions taken or to be taken.

- Any suspension or termination of IRB approval of research.
- Any significant noncompliance with HRPP procedures or other requirements.

Immediately (within 24 hours):

- Any suspected or confirmed compromise of personally identifiable information, with a description of any corrective actions taken or to be taken. The incident must also be immediately reported to the DOE-Cyber Incident Response Capability.
- Any serious adverse event, with a description of any corrective actions taken or to be taken.

The Director ensures that all steps of this policy are completed within 30 days of the initiating action. For more serious actions, the Director will expedite reporting.

22 Investigational Drug and Device Research

22.1 *Purpose*

The following procedures describe the policy relating to the use of investigational drugs and devices in research under the auspices of UCD and/or Affiliates. Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA and VA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, other applicable FDA regulations, and applicable VHA regulations.

22.2 *Definitions*

Investigational Drug. An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

Investigational Device. Is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

Emergency Use. Emergency use is defined as the use of an investigational drug or biological product with 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 COMIRB approval.

Significant Risk (SR). Significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety,

or welfare of a subject; or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR). A non-significant risk device is an investigational device other than a significant risk device.

Humanitarian Use Device (HUD). Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 8,000 individuals in the United States per year, and is approved by the FDA as a Humanitarian Use Device.

22.3 *FDA Exemptions*

The following categories of clinical investigations are exempt from the requirements of FDA regulations for COMIRB review:

- 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. [21 CFR §56.104(c)]
- 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. [21 CFR §56.104(d)]
- Clinical investigations using drugs that meet all of the criteria for exemption from the IND regulations set forth in 21 CFR 312.2(b).
- Clinical investigations of devices that meet one of the criteria for exemption from the IDE regulations set forth in 21 CFR 812.2(c), unless data will be submitted to the FDA in support of device marketing or development.

22.4 *IND/IDE Requirements*

When the principal intent of the investigational use of a test article is to develop information about the product's safety or effectiveness, an Investigational New Drug (IND) or Investigational Device Exemption (IDE) may be required.

Investigators will be asked on the COMIRB application to indicate whether the research involves drugs or devices. If so, and the study does not meet the exemption criteria from the IND/IDE regulations, they will be asked if there is an IND/IDE for the research. If there is, they will be asked for evidence of the IND/IDE, which could be a:

- Industry sponsored protocol with IND/IDE
- Letter from FDA
- Letter from industry sponsor

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination for COMIRB review. If the FDA has determined that the study is NSR, documentation of that determination must be

provided; an FDA determination supersedes any determination by COMIRB.

If the research involves drugs or devices and there is no IND/IDE, the investigator will be asked for a rationale as to why it is not required.

The COMIRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

For research that requires an IND or IDE, COMIRB will formally review the application after confirmation with the IND-IDE Office (IIO) that the IND/IDE has been submitted. If COMIRB's approval occurs inside of 30 days from IND submission, COMIRB will confirm the status of the IND submission with the IIO and include a condition not to start the research prior to 30 days of the IND submission unless the IIO has received early approval from the FDA. If the FDA issues a hold or recommends changes to the protocol, the IIO will inform COMIRB. COMIRB and the IIO will communicate directly with the study team as appropriate to ensure the study is not opened to accrual prior to final FDA approval.

22.4.1 IND Exemption

For **drugs,** an IND may not be necessary if **all** seven of the following conditions are met:

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for COMIRB review and informed consent [21 CFR parts 56 and 50, respectively];
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7];
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Note: The following are also exempt from the IND requirements : (a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and (b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

1. It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
2. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

3. It is shipped in compliance with 312.160

22.4.2 IDE Exemption

For devices, an IDE may not be necessary if:

1. The research involves a device when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    - Is noninvasive,
    - Does not require an invasive sampling procedure that presents significant risk,
    - Does not by design or intention introduce energy into a subject, and
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk. Note: COMIRB interprets "a combination of two or more devices in commercial distribution" to mean two or more FDA-approved devices used in tandem for an untested purpose. COMIRB considers head-to-head comparisons of FDA-approved devices which are all investigated in accordance to their FDA-approved labeling to be exempt from IDE regulations under 21 CFR 812.2(c)(1)or(2) (i.e., #1 or #2 above).;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 8 12.5(c);
7. The research involves a custom device as defined in 21 CFR 8 12.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

22.4.3 NSR determination

For devices that require a NSR risk determination, a full-board convened meeting with make the determination of SR or NSR and COMIRB will follow the FDA guidance provided in the ‘Information Sheet Guidance for IRBs, Clinical Investigators and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies’, p. 7, section A ‘For a device study to be eligible for expedited review, it must be an NSR study AND present no more than minimal risk to the subject (21 CFR 56.110). These studies will be expedited under category 1(b).

22.5 *In Vitro Diagnostic Product (IVD)*

In vitro diagnostics (IVDs) meet the definition of a device under the Act. Section 201(h) of the Act defines a device as:

"an instrument, apparatus, implement, machine, contrivance, implant, **in vitro reagent,** or other similar or related article, including any component, part or accessory, which is
1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them.
2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals, or
3) intended to affect the structure or any function of the body of man or other animals, and

Which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. 321(h).

COMIRB will follow FDA guidance on determining if the study of an IVD is exempt from the IDE regulations or if it is a significant or non-significant risk study under 21 CFR 812.2(b).

22.6 *Responsibilities in Drug/Device Research*

22.6.1 Investigator Responsibilities

- The investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines and must obtain approval from the COMIRB.
- The investigator must complete and submit Attachment C or D and provide information on the plan for storage, security and dispensing of the drug or device to the COMIRB and, prior to its approval of the study. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of investigator's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation. The Eastern Colorado HealthCare System R&D or Affiliate safety committee also reviews and approves the planned dispensing and storage of the drug or device.
- Each of the Affiliates also has an internal review process for approving and monitoring biologics and devices. For research at the Eastern Colorado HealthCare System, it is the R&D Committee.
- The investigator is responsible for the investigational drug/device accountability which includes storage, security, dispensing, administration, return, disposition and records of accountability. Whenever possible, the investigator will delegate the responsibility for drugs/biologic accountability to the Affiliate pharmacy. Any exceptions will be reviewed by COMIRB on a case by case basis in collaboration with the UCD Product Review .
- The investigator is responsible for reporting all unexpected fatal or life-threatening suspected adverse reactions associated with the use of an investigational drug/device to the FDA within 7 calendar days after determination; suspected adverse reactions or similar events within 15 calendar days. The investigator is responsible for notifying the sponsor as specified in the protocol.

- For research involving investigational new drugs:
    - Approval from the appropriate Affiliate safety committee must be obtained.
    - The PI is responsible for informing the Affiliate Pharmacy Service that COMIRB approval has been obtained.
    - The PI must inform the Affiliate Pharmacy Service when a study involving investigational drugs has been terminated.
    - For research at the Eastern Colorado Health Care System, the investigator must comply with all regulations regarding the use of the Pharmacy Service.
- For research involving investigational devices:
    - If a device considered NSR by the investigator or sponsor, is determined to have significant risk upon COMIRB review, the investigator is responsible for notifying the sponsor of the COMIRB's determination upon receipt of written notice. The sponsor in conjunction with the PI can either provide additional justification for why the device should be considered NSR or provide correspondence from the FDA detailing the FDA's assessment.
    - The PI must work with the affiliate hospital in accordance with hospital policy relating to the storage, dispensing and logging of devices.
    - Following completion of the study the affiliate hospital termination procedure for investigational drugs or devices must be followed.
    - When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor and will comply with the regulatory responsibilities of a sponsor.
- The UCD Research Quality Assurance and Education Program will work with the sponsor / investigator to ensure that they understand the role as sponsor / investigator and will conduct periodic audits.

22.6.2 COMIRB's Responsibilities

- The COMIRB must review the research in accordance with these requirements and needs to use the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
- For research involving investigational devices:
    - Unless the FDA has already made a risk determination for the study, the COMIRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The determination of risk must be made by a convened panel. The panel must consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If

the study that has been submitted as NSR is considered SR, the IRB must recommend that an IDE be obtained.
- Protocols involving Significant Risk devices do not qualify for expedited review.
- The COMIRB must document in the Minutes the rationale for the determination of a device that is classified as NSR/SR.
- The COMIRB will provide written documentation of approval to the investigator with a determination of whether the device presents a significant or non-significant risk.
- If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.
- The panel has the responsibility to review the information in the application form to ensure that the test article will be used only by authorized individuals in individuals who are subjects in the research protocol.
- The panel has the responsibility to review the information provided in the application form to ensure that the test article will be appropriately stored, dispensed and disposed.
- The panel may request that the UCD Investigational Product Review Committee (IPRC) approve the product management plan prior to approving the study. Generally the approval and recommendations of the IPRC must be in place before a study can enroll subjects.
- The panel makes the determination that a study is an applicable clinical trial under the regulations. Researchers are advised at the time of IRB review of the requirements for posting on the National Library of Medicine site, ClinicalTrials.gov. When notified, PIs may contact CRAO for help in setting up an account, setting up a record, and subsequent responses to reviews and other posting requirements. Biostatistical support is available to assist researchers enter results.

- **Applicable Clinical Trial**
  - Applicable Drug Clinical Trial: COMIRB adopts the definition of an applicable clinical trial based on FDAAA as "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act. COMIRB also adopts the definition of FDAMA (Food and Drug Administration Modernization Act), specifically Section 113-Information Program on Clinical Trials for Serious and Life-Threatening Diseases, "requires the US Department of Health and Human Services, through the National Institutes of Health, to establish a registry of clinical trials both federally and privately funded trials of experimental treatments for serious or life-threatening diseases".
  - Applicable Device Clinical Trial: COMIRB adopts the definition of this term as provided in the Food and Drug Administration Amendments Act (FDAAA) and defines the term as 1) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food Drug, and Cosmetic Act against a control in human subjects if it meets four criteria a) it is a prospective clinical study of health outcomes; b) it compares an

intervention with a device against a control in human subjects; c) the studies device is subject to section 510(k), 515 or 520(m) of the Federal Food, Drug and Cosmetic Act (FDC Act); and d) it is other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not health outcomes.

COMIRB Senior IRB staff will make the determination of whether a study meets the definition of an applicable clinical trial. This will be noted in the final minutes of the panel meeting and will be flagged in InfoEd under the legacy variables.

22.7 *Emergency Use*

22.7.1 Emergency Exemption from Prospective COMIRB Approval

FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which not standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval. Also the activity cannot be a systematic investigation designed to develop or contribute to generalizable knowledge. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective COMIRB approval found at 21 CFR 56.104(c) may be utilized.

Informed consent and documentation of consent in accordance with FDA regulations 21 CFR 50.20, 25, 27 are required unless the criteria for the exception to the requirement for consent are met. The COMIRB must be notified within 5 working days when an emergency exemption is used. COMIRB defines one use per institution as one use per legal entity. Subsequent use of the same test article on a different patient at the same institution (legal entity) would be subject to COMIRB review by the full board.

The required documents to be submitted by the physician for COMIRB review of this process are outlined on the COMIRB website. The internal process for reviewing the use of the investigational drug or biological product in this situation is outlined in the COMIRB standard operating procedure SOP CP-012– Emergency Use.

22.7.2 Emergency Exemption from Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

a. The subject is confronted by a life-threatening situation necessitating the use of the test article;
b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
c. Time is not sufficient to obtain consent from the subject's legally authorized representative;
d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing

by an independent physician within 5 working days. The emergency use must be reported to the COMIRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the COMIRB. A panel Chair will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations. [Detailed procedures are described on the COMIRB website.]

22.7.3 Expanded Access uses of investigational drugs: Individual patient IND, Intermediate size patient IND or Treatment IND

FDA regulations (21 CFR 312 Subpart I) aims to facilitate the availability of investigational drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

The following definitions of terms apply:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Documentation to the FDA.

An expanded access submission is required for each type of expanded access. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND, if the sponsor of the existing IND grants a right of reference to the IND.

The physician must provide the following:

(1) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;
(2) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;
(3) The method of administration of the drug, dose, and duration of therapy;

(4) A description of the facility where the drug will be manufactured;
(5) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;
(6) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and
(7) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

Individual Patient Expanded Access (sIND):
The licensed physician must request and recieve sIND from the FDA prior to treatment, according to FDA regulations and guidance. The IND/IDE Office provides assistance with this in most cases.

If the physician requests a waiver of full IRB review on Form 3926, treatment will be allowed to proceed following concurrence from an IRB chairperson or another designated IRB member. In accordance with FDA Guidance, *Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products* (September 2023), waiver of full IRB review also extends to any changes or amendments to the original treatment plan or for continuing review of the individual expanded access request.

If a waiver of full IRB is not requested, IRB approval must be obtained prior to treatment

At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a final report. The IND/IDE Office follows up with physicians as necessary.

Intermediate-size expanded access

FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. FDA may ask a sponsor to consolidate expanded access under this section when the agency has received a significant number of requests for individual patient expanded access to an investigational drug for the same use.

Expanded access maybe needed in the following situations:
(1) The drug is not being developed, for example, because the disease or condition is so rare that the sponsor is unable to recruit patients for a clinical trial.
(2) The drug is being studied in a clinical trial, but patients requesting the drug for expanded access use are unable to participate in the trial. For example, patients may not be able to participate in the trial because they have a different disease or stage of disease than the one being studied or otherwise do not meet the enrollment criteria, because enrollment in the trial is closed, or because the trial site is not geographically accessible.
(3) The drug is an approved drug product that is no longer marketed for safety reasons or is unavailable through marketing due to failure to meet the conditions of the approved application, or the drug contains the same active moiety as an approved drug product that is unavailable through marketing due

to failure to meet the conditions of the approved application or a drug shortage.

FDA must determine that there is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive the drug under expanded access; and there is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded-access use a reasonable therapeutic option in the anticipated patient population.

Treatment IND or treatment protocol.
FDA may permit an investigational drug to be used for widespread treatment use. When a drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed; and the sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence; and when the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. Such evidence would ordinarily consist of data from phase 3 trials, but could consist of compelling data from completed phase 2 trials; or when the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury. This evidence would ordinarily consist of clinical data from phase 3 or phase 2 trials, but could be based on more preliminary clinical evidence. The sponsor is responsible for monitoring the treatment protocol to ensure that licensed physicians comply with the protocol and the regulations applicable to investigators.

Role of COMIRB
Use of the investigational drug for an individual patient IND, Intermediate size patient IND or Treatment IND must meet all applicable FDA requirements and must be submitted to COMIRB for review and approval. All applicable regulations must be met including those at 21 CFR Parts 50 and 56.

The PI should submit a copy of all documentation submitted to the FDA, a copy of the letter granting the IND, any other communication with the FDA as well as all documentation required for an initial submission for full board review. Per FDA guidance (Expanded Access to Investigational Drugs for Treatment Use, June 2016, updated October 2017), for single-patient IND protocols that request a waiver of full-board review, a Chair, or an experienced IRB member designated by a Chair, can review and provide concurrence prior to the treatment begins in lieu of obtaining IRB review and approval at a convened IRB meeting.

In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports to FDA.

22.8 Compassionate Use of an Investigational Device

UCD and Affiliate policy is based on the FDA guidance document entitled:
"Guidance on IDE Policies and Procedures" (January 20, 1998

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm)

FDA may permit the use of an investigational device in a human subject under circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition. In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. Also the activity cannot be a systematic investigation designed to develop or contribute to generalizable knowledge. If these criteria are met, then compassionate use procedure may be utilized.

The compassionate use procedure may be utilized only with an investigational device; there is no provision for compassionate use of an investigational drug or biologic.

Informed consent and documentation of consent in accordance with FDA regulations 21 CFR 50.20, 25, 27 are required. Waiver of informed consent is not permitted for compassionate use of an investigational device. The COMIRB must be notified within 5 working days when the compassionate use procedure is used. This notification must not be construed as an approval for the compassionate use by the COMIRB. A COMIRB panel Chair will review the report to verify that circumstances of the compassionate use conformed to FDA guidance.

[The required documents to be submitted by the physician for COMIRB review of this process is outlined on the COMIRB website. The internal process for reviewing the use of the investigational device in this situation is outlined in the COMIRB standard operating procedure SOP: Compassionate Use of Devices]

A patient safety monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any unanticipated problems occurred as a result of device use, these should be discussed in the supplement and reported to the COMIRB as soon as possible. A follow-up report must be submitted to the COMIRB within twelve months of the use of the device, or sooner if required by FDA.

Any subsequent use of the test article at the institution is subject to FDA review. FDA may allow the treatment of additional patients by way of the compassionate use procedure, or may require prospective IRB approval of a Treatment IDE protocol.

22.8.1 Emergency Waiver of IND or IDE

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug or device to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug or device for a specific use in such a circumstance in advance of submission of an IND or IDE. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent and documentation of consent are required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

22.8.2 Humanitarian Use Device (HUD)

In accordance with 21 CFR 814.124, treatment with a HUD is subject to full board initial

review by the COMIRB [and the R&D Committee for the Denver VAMC or Affiliate safety committee] and is eligible for continuing review under expedited procedures. COMIRB's policy on use and investigation of HUDs follows the FDA guidance "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" (July 8, 2010).

Multiple sites can be approved under one protocol for the use of a HUD among UCD and its Affiliates; however the separate ordering, procurement and storage plans for each site must be clearly delineated in the application form. The device can only be used at the institution that was responsible for ordering or storing of the device. Addition of a second site requires a separate IRB protocol submission. At the time of review, the COMIRB will determine if written consent from participants for use of the HUD is necessary. If a physician in an emergency situation determines that COMIRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior COMIRB approval. In this instance, the investigator is required to provide written notification of the use to the COMIRB within five days after use of the device in accordance with COMIRB's emergency use policy above.

[Note: if conducted at the Denver VAMC, approval must be obtained from the Chief of Staff.]

It is the responsibility of the investigator to notify the FDA if the COMIRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval.

Investigators are reminded that Humanitarian Use Devices are a special class of FDA-approved device. They can be used to treat patients only with prior IRB approval. COMIRB must approve all uses, whether on-label or off-label, described in the protocol before the devices are used. If HUDs are to be used off-label (considering indications/populations for use and how the HUD is used/applied), the investigator must provide information to COMIRB so that the panel can determine how the off-label use of the HUD changes risks to patients. Use of an HUD can involve no collection of safety or effectiveness data (other than the required reporting of Unanticipated Problems to COMIRB and the Sponsor/FDA).

If safety and effectiveness data are collected on an HUD, a clinical investigation of the device is occurring. In this case, COMIRB will consider the protocol in relation to the IDE requirements described above. When HUDs are investigated strictly according to their FDA labeling (considering indications/populations for use and how the HUD is used/applied), the investigations will usually be exempt from IDE regulations.

22.8.3 Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived is covered by 21 CFR 50.24 and OPRR Reports, document Number 97-01, October 31, 1996.

Under CFR §50.24 for research not subject to FDA regulation this is covered by OPRR Report, number 97-01 "Informed consent requirements in emergency research". The research plan must be approved in advance by the FDA or DHHS (as applicable) and the COMIRB, and publicly disclosed to the community in which the research will be conducted. Such studies are not allowed under the regulations covering the emergency

use of a test article in a life-threatening situation (21 CFR §56.104).

Prior to submission of any protocol, the PI must contact the COMIRB Director to discuss the protocol. A meeting of all interested parties will be convened including:

- PI and research team
- COMIRB Director and panel Chair(s)
- Other members of the UCD HRPP
- Affiliate compliance office and risk management
- Member(s) of the CCTSI Community Engagement Core

The aim of the meeting is to determine the feasibility of the proposal based on the resources and the commitment of the Affiliate institution. Also to develop a time line and implementation plan which will include all the elements as directed in the FDA and DHHS regulations. The protocol will then be submitted to COMIRB for full board review including the proposed implementation plan.

22.8.3.1 Limitations of the Emergency Research Exception from Informed Consent

The waiver is explicitly excluded when the research involves certain protected research populations including:

- Fetuses, pregnant women, and human in vitro fertilization (Subpart B of 45 CFR 46)
- Prisoners (Subpart C of 45 CFR 46)
- Planned emergency research under 21 CFR 50.24 cannot be conducted by the VA

22.8.3.2 Documents for Approval of the Emergency Research Exception from Informed Consent

In addition to all the documents required for an initial review as detailed in section 12 above, the IRB requires the following documents:

- Copy of specific FDA IND or IDE approval letter (if FDA regulated) for a protocol detailing a plan to utilize waiver of consent in emergency research;
- Justification by PI for needing a waiver of consent for emergency research based on the criteria detailed below.
- Plan for Community Consultation - Before the community engagement plan is submitted to the IRB for review and approval it must first be reviewed and approved by the CCTSI Community Engagement Consultation Service.

22.8.3.3 Criteria for Approval of Emergency Research Exception from Informed Consent

The IRB panel must determine that the research requesting waiver for emergency research meets the criteria for approval, as detailed in OPRR Report, number 97-01 for OHRP regulated research and in 21 CFR 50.24 for FDA regulated research. Specifically, the IRB panel must determine that:

a. The human subjects are in a life-threatening situation; available treatments are unproven or unsatisfactory. In addition, the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
b. Obtaining informed consent is not feasible because: i) the subjects will not

be able to give their informed consent as a result of their medical condition, ii) the intervention involved in the research must be administered before consent from the subjects' legally authorized representative is feasible, and iii) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

c. Participation in the research holds out the prospect of direct benefit to the subjects because i) subjects are facing a life threatening situation that necessitates intervention; ii) appropriate animal and other preclinical studies have been conducted and the information derived from those studies, and related evidence, supports the potential for the intervention to provide a direct benefit to the individual subjects; iii) risks associated with the research are reasonable in relationship to what is known about the medical condition of the potential class of subjects, and the risks and benefits of standard therapy, if any, and of what is known about the risks and benefits of the proposed intervention or activity
d. The research could not practicably be carried out without the waiver.
e. The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence. The investigator has committed to attempting to contact a legally authorized representative for each subject within the window of time and, if feasible, to asking the legally authorized representative contacted for consent within the window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.
f. The IRB must review and approve the informed consent procedures and an informed consent document in accord with sections 46.116 and 46.117 of 45 CFR 46. 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 must review and approve procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research.
g. 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 research will be conducted, as well as communities from which the subjects will be drawn; ii) public disclosure including the plans for the research and its risks and expected benefits to the communities in which the research will be conducted and from which the subjects will be drawn before initiation of the research, iii) public disclosure of sufficient information after completion of the research 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 research; 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 research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of

continuing review.

h. The IRB must ensure 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 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 the family member, if feasible. For research subject to DHHS requirements, for the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; 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.
i. When the research is not subject to FDA regulation, but follows DHHS regulations, the IRB will find, document, and report to DHHS that the above conditions have been met relative to the research, and that the research is not subject to regulations codified by the FDA at 21 CFR 50.
j. Additionally for FDA regulated research:
    - The IRB must document that a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation concurs that the waiver of consent is allowable. This concurrence must be documented in the meeting minutes
    - If the IRB determines that it cannot approve a protocol involving a waiver of consent either because it does not meet the requirements of the regulations or because of other relevant ethical concerns, it must provide documentation of this decision promptly to the researcher and the sponsor of the research. The sponsor must promptly disclose this information to the FDA and to other researchers who are conducting or have been asked to conduct this or similar protocols, and to other IRBs that have been, or are, asked to review this or similar protocols by that sponsor.

22.8.3.4 Documentation by the IRB

The IRB panel will use the "Exception from Informed Consent (EFIC) Checklist: Community Consultation and Public Disclosure" to guide their review for approval of Waiver of Consent in an Emergency Setting.

Initial IRB approval allows the investigator to conduct the community engagement

plan proposed and approved by the IRB panel. A summary of the feedback from the community must be submitted to the IRB for review and approval. The IRB panel will review the feedback from the community and determine if recommendations made by the community should be incorporated into the consent process or research implementation. Enrollment on an approved protocol cannot begin until the IRB has reviewed the recommendations of the community engagement and determined that it is still appropriate for the study to be approved.

Closure: Before a study using waiver of consent in an emergency setting can be closed, the IRB panel must review and approve the plan for public disclosure including the study findings and feedback on the implementation of the protocol to the community.

22.8.3.5 DoD Requirements for Waiving the Advance Informed Consent Provision of 10 USC 980

When conducting emergency medicine research supported by DoD and involving a human being as an experimental subject (research qualifying for exception from informed consent under 21 CFR 50.24 or a waiver of informed consent under 45 CFR 46.101[i]), a waiver of the advance informed consent provision of 10 USC 980 must be approved by the DoD Office for Human Research Protections (DOHRP) on behalf of the Secretary of Defense before IRB approval may be granted. The Principal Investigator is responsible for initiating this request by contacting the DoD Program Officer/sponsoring DoD component's Office of Human Research Protections (COHRP), which submits the waiver request through DoD component-level administrative review to DOHRP. The PI must provide documentation of the DOHRP written approval to COMIRB in order to receive IRB approval.

These provisions apply only to non-exempt research involving a human being as an experimental subject, defined in DoD Instruction 3216.02 as “[a] n activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of Section 980 of Title 10, U.S.C.; it does not affect the application of Part 219 of Title 32, CFR.

23 HIPAA (Health Insurance Portability and Accountability Act)

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. A subsequent omnibus rule revised the final rule again in January 2013, with a compliance deadline of September 23, 2013. While the main impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research. Researchers, COMIRB staff and members as well as research administration must be aware of these regulations.

23.1 *Historical Background*

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is an expansive federal law, only part of which is intended to protect the privacy of health care information. HIPAA

required Congress to enact a health information privacy law by August 1999 and stated that if it did not act by then, which it did not, the U. S. Department of Health and Human Services (DHHS) must develop privacy regulations. The final Privacy Rule was published on August 14, 2002, and further revised in January 2013.

The objective of the rule is to protect the privacy of an individual's health care information. It creates a federal "floor" of protection so that every person in this country has at least the same basic rights and protections, though some may have additional rights depending on state law.

23.2 *Patient Rights and Research*

Under HIPAA, patients have certain rights. Those that may affect research include the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain disclosures of PHI that occur outside the scope of treatment, payment and health care operations that have not been authorized.

23.3 *Research under HIPAA Regulations*

Investigators that are part of a **covered entity** conducting **research** using "**Protected Health Information**" (**PHI**) must comply with HIPAA regulations.

23.4 *Covered Entities*

The majority of healthcare schools, centers, and departments within UCD and its affiliates function as covered entities under HIPAA.

The UCD - Downtown Campus is generally not a covered entity under HIPAA.

Covered entities are health plans (e.g. health insurance issuers), health care clearinghouses (e.g. healthcare billing company), and healthcare providers who electronically transmit health information in connection with eight transactions. Generally, these transactions concern DHHS billing and payment for services or insurance coverage. Covered entities can be institutions, organizations, or persons.

23.5 *Privacy Board*

COMIRB also acts as the Privacy Board for HIPAA-related research issues for UCD and the Affiliate Hospitals. It also serves as the Privacy Board for protocols reviewed by an external IRB if that IRB is not acting as the privacy board. The applicable designation will be outlined in the accompanying MOU/ Reliance Agreement or IAA.

A Privacy Board is a review body established to act upon requests for a waiver or an alteration of the HIPAA Authorization requirement under the HIPAA Privacy Rule for uses and disclosures of protected health information (PHI) for a particular research study. In this capacity COMIRB may approve a complete or partial HIPAA waiver, and the Privacy Board also receives and considers reports of possible HIPAA-related problems, such as the use of PHI without an appropriate HIPAA authorization or waiver. Institutional oversight of the authorization forms, when needed, for protocols with an external IRB of Record has been delegated to the External IRB coordinators.

23.6 *HIPAA Definitions*

Research - systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. *This definition is identical with the*

one used in the DHHS "Common Rule", separate federal legislation designed to protect human subjects involved in research. HIPAA describes privacy standards for protecting PHI and so applies to research that involves humans' health information.

PHI – Protected Health Information. Health information – any information recorded about past, present, or future physical or mental health or condition of an individual, or the past, present, or future payment for the provision of healthcare to an individual. Health information may be oral, print or electronic.

Individually identifiable information:

- Name
- Postal address (geographic subdivisions smaller than state)
- All elements of dates, except year (birth date, if over 89, must be aggregated)
- Phone number
- Fax number
- Email address
- Social security number
- Medical record number
- Health plan number
- Account numbers
- Certificate/license numbers
- URL
- IP addresses
- Vehicle identifiers
- Device ID
- Biometric ID
- Full face/identifying photo
- Any other unique identifying number, characteristic, or code

PHI does not include de-identified health information. De-identified information is information that does not identify an individual and for which there is no reasonable basis to believe that information could be used to identify an individual.

PHI does not include individually identifiable health information found in education records covered by FERPA ("Family Educational Rights and Privacy Act"), records described at 20 U.S.C. 1232g(a)(4)(B)(iv) (higher education student medical records) and employment records held by the University in its role as employer.

Unlike the "Common Rule" regulations, HIPAA regulations also cover research involving deceased individuals. Decedent research involving PHI must be cleared through UCD's Privacy Officer prior to implementation. The researcher must certify that the access/use of PHI is solely for research involving deceased individuals, all individuals are deceased, and the PHI is necessary for the conduct of the research through a Deceased Research Certification Form.

23.7 *HIPAA and Existing Studies*

Human subject research protocols that were approved after April 14, 2003, must have HIPAA authorizations, a HIPAA waiver, or Data Use Agreement in place. Individuals consented or re-consented into a human subject research protocol after April 14, 2003 must sign an authorization.

Any research subject enrolled in a human subject research protocol that uses PHI from a covered entity must sign a HIPAA-compliant authorization form, unless a waiver has been obtained. This form is in addition to the existing Informed Consent document and is federally

required. In some cases, the Informed Consent document may be combined with the HIPAA authorization.

23.8 *HIPAA Documentation*

HIPAA documents include HIPAA Authorization Forms, combined consent/authorization forms, the HIPAA Waiver Request (Attachment O), Pre-Research Certification, Data Use Agreement, and Notice of Privacy Practices.

23.9 *HIPAA Language / Authorization Forms*

Note: for VA regulated research only, the HIPAA authorization form must be separate from the informed consent document.

Use and disclosure of PHI requires a valid authorization. Authorizations must contain the following elements:

- Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner)
- The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure.
- The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure.
- Description of each purpose of the requested use or disclosure. NOTE: Researchers should note that this element must be research study specific, not for future unspecified research.
- Authorization expiration date or event that relates to the individual or to the purpose of the use or disclosure (the terms “end of the research study” or “none” may be used for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the Authorization is signed by an individual’s personal representative, a description of the representative’ authority to act for the individual.

The Authorization must include the following required statements:

- Notice of the covered entity’s ability to deny research-related treatment or limit enrollment in a study unless an authorization is provided to use or disclose the PHI for the research;
- A statement that the potential exists for information disclosed via the authorization to be subject to redisclosure by the recipient of the information and therefore no longer protected by HIPAA.
- The Authorization must be written in plain language. A copy of the signed Authorization must be provided to the individual signing it.
- A research subject may revoke an authorization at any time, provided that the revocation is in writing, except to the extent that the covered entity has taken action based on the authorization and prior to notice of revocation. If revoked, the authorization is not valid and may not be used.

Authorization for optional study procedures:

- If the study plan allows subjects to consent to optional, additional research procedures outside of the main study procedures, the authorization for these optional procedures must be separate from the authorization for the main study procedures. Authorization

for main study procedures and optional study procedures may be obtained with the same form (known as a compound authorization), as long as the authorization for each is distinct, and the authorization for the main study is not contingent on authorization for the optional procedures.

COMIRB is responsible for reviewing the HIPAA Authorization Forms prepared by the investigator. The wording on the HIPAA Authorization Form must contain all of the required elements and meet all other requirements as described in this section. If the language on the HIPAA authorization template has been altered, COMIRB should consult the Privacy Officer to ensure that the authorization meets all the UCD requirements. If the HIPAA authorization is revised during the protocol approval period, COMIRB must review the revised document at least by the time of the subsequent continuing review.

23.10 *HIPAA Waiver of Authorization*

COMIRB may approve a waiver of individual HIPAA authorization required under 45 CFR 164.508 if the IRB or an IRB reviewer determines that the waiver satisfies the following three criteria:

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

(1) an adequate plan to protect the identifiers from improper use and disclosure;

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

(3) 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 subpart;

(B) The research could not practicably be conducted without the waiver or alteration; and

(C) The research could not practicably be conducted without access to and use of the PHI.

The “plans” and “written assurances” noted above are components of the COMIRB application form.

The IRB reviewers will use the HIPAA Waiver checklist to guide their reviews. The checklist is made available to IRB reviewers as a stand-alone document and as a component of other checklists. Approval of the waiver of individual HIPAA authorization is signed by the IRB reviewer, either on a checklist or as part of their electronic review.

For VA research only: A copy of the completed HIPAA Waiver checklist or VHA Form 10-0521 is collected by the VA Research Office with the approved documents as part of the packet for R&D review.

The COMIRB approval letter will document the date of approval of the waiver, include a statement that the waiver satisfies the three criteria of the Privacy Rule, and indicate the manner of review. The approved COMIRB application form will document whether the waiver was requested for all or part of the study, and include a brief description of the PHI for which use or access is appropriate under the waiver.

23.11 *Pre-Research Certification*

Researchers who need access to UCD or an affiliated hospital or research center's medical records, databases or tissue repositories to use PHI of individuals to assess the feasibility of conducting a study, to design a research study, or to formulate a research hypothesis must submit the Pre-research Certification Form to custodian of the information to be accessed and to the Privacy Officer. PHI accessed in this manner may not be used to recruit subjects.

23.12 *Treatment INDs or single-patient INDs*

For protocols submitted to COMIRB under a treatment IND or a single-patient IND protocol, COMIRB will consider HIPAA authorization per the treatment, payment, and health care operations (TPO), which permits use and disclosure of PHI for clinical care purposes. If the submission requires the collection of data for the sponsor, outside of safety data, the submission will be reviewed as research and research HIPAA authorization will be obtained.

23.13 *Data Use Agreement*

Researchers may use specific indirect identifiers, also known as a limited data set, through a Data Use Agreement.

A limited data set removes the following identifiers of the individual, or of the relatives, employers, or household members of the individual have been removed:

a) Names;
b) Postal address information, other than town and city, State, and zip code;
c) Telephone numbers;
d) Fax numbers;
e) Electronic mail addresses;
f) Social security numbers;
g) Medical record numbers;
h) Health plan beneficiary numbers;
i) Account numbers;
j) Certificate/license numbers;
k) Vehicle identifiers and serial numbers, including license plate numbers
l) Device identifiers and serial numbers;
m) Web Universal Resource Locators (URLs);
n) Internet Protocol (IP) address numbers;
o) Biometric identifiers, including finger and voice prints; and,
p) Full face photographic images and any comparable images.

A formal agreement known as a Data Use Agreement must be in place between the covered entity that holds the information and the recipient of the information. The data use agreement must identify who will receive the limited data set, establish how the data may be used and disclosed by the recipient, and provide assurances that the data will be protected. The Privacy Officer should be contacted to ensure that an appropriate document is put in place. The Associate Vice Chancellor for Regulatory Compliance is designated signature authority for UCD. If the covered entity learns that the researcher has violated this agreement, the entity must take reasonable steps to end or repair the violation and, if such steps are unsuccessful, stop disclosing PHI to the researcher and report the problem to the Privacy Officer and as needed to DHHS Office of Civil Rights.

No Authorization or Waiver of Authorization is required for the covered entity to use or disclose a limited data set.

23.14 *Notice of Privacy Practices*

UCD and/or the affiliated hospital or research center must provide its Notice of Privacy Practices to all individuals who are patients, human research participants, or enrollees in a group health plan of UCD. The principal investigator is responsible for ensuring that research subjects have received, at some time, the Notice of Privacy Practices as applicable under HIPAA. Inmates may be given the Notice of Privacy Practices document but there is no requirement under HIPAA to provide inmates with this document.

24 Student Records

The Family Educational Rights and Privacy Act (FERPA) (See 20 U.S.C. § 1232g; 34 CFR Part 99) governs the disclosure of student records and access to student records by parents and eligible students. FERPA applies to all public elementary and secondary schools as well as post-secondary institutions that receive federal funding through the Department of Education. UCD is subject to FERPA.

FERPA distinguishes between two classes of information:

> **Directory information** is information in an educational record "that would not, generally, be considered harmful or an invasion of privacy if disclosed." Institutions covered by HIPAA define what data they consider to be directory information. At UCD, directory information includes the student's name, address, telephone number, major, enrollment status, and activities. Each University campus has established a student rights and records policy that can be found on its registrar's web site.
>
> **Other information** contained in education records.

"Education records" are defined under FERPA as records that directly relate to a student and are maintained by an educational agency or institution, or a third party on their behalf.

"Education records" generally do not include: records maintained by law enforcement units, such as the University's Department of Public Safety; employment records related to students in their capacity as employees and where the employment is not a result of the person's status as a student; medical records made by a physician, psychiatrist, psychologist or other health professional for treatment of the student and disclosed only to individuals providing the treatment; and records that only contain information about the individual after he/she is no longer a student at the institution.

An educational institution may disclose directory information if it has given public notice to parents and eligible students (i.e., students who are 18 or older or are attending postsecondary education institutions) regarding the types of information included in the institution's definition of "directory information" and the right to opt out of disclosure of any or all types of directory information. Parents' rights automatically transfer to the student once the student becomes an "eligible" student. If a parent or eligible student declines to opt out, then the institution may disclose directory information without the student's specific consent. At UCD, only the student and not the parents has the right to access a student's file; opt out of a directory listing; or authorize disclosure of student record information. An institution may also disclose the directory information of former students without notification.

Before an educational institution discloses personally identifiable non-directory information from a student record, the parent or eligible student must provide a signed and dated authorization for the disclosure. The authorization must specify the records to be disclosed; state the purpose of the disclosure; and identify the person to whom the disclosure is to be made. The

authorization may be in electronic form. Written authorization is necessary only if the information contains personally identifiable information such as, but not limited to, the student's name or a parent's name; an address; a social security or student number; or a list of personal characteristics that would enable identification of a student.

There are a number of situations where FERPA allows disclosure of individually identifiable information without prior written authorization. These include disclosure to other school officials with legitimate educational interests; to officials at other schools where the student seeks to enroll; to various state or federal officials; for the purpose of determining or implementing financial aid; and to organizations conducting studies for, or on behalf of, educational agencies or institutions. This last exception is the most important for research considerations.

The exception for research activities conducted on behalf of educational institutions is limited.

The exception for research activities applies to research to develop, validate and administer predictive tests, to administer student aid programs, or to improve instruction. Research organizations must use the data provided only for these stated research purpose(s). Academic records may be disclosed only if a study is conducted and reported in such a way as to prevent personal identification of parents or students by individuals not associated with the researcher.

Any personal information used in the study must be destroyed when it is no longer needed for the study. A research organization that violates these requirements will be banned from accessing individually identifiable educational records for at least five years. In addition, a research organization that receives educational record information from an educational agency without the parent's or eligible student's prior consent is prohibited from re-disclosing that information.

FERPA only protects education records. These are records that are directly related to a student and are maintained by an educational agency. This does include records of the law enforcement unit of the educational agency, employment records other than records of individuals employed as a result of their status as students, or records containing information about an individual after he or she is no longer a student at that institution. Finally, records of an eligible student made or maintained by a physician, psychiatrist, psychologist or other health professional in connection with treatment of the student are not educational records.

The definition of an education record requires that the record is related to a student. FERPA defines a student as "any individual who is or has been in attendance at an educational agency or institution and regarding whom the agency or institution maintains education records."

Thus, an application for admission alone is not an educational record. On the other hand, the application of an accepted student who attends the educational institution appears to be an educational record. The application remains protected by FERPA even after the student graduates. FERPA requires that the institution keep a record of each request for access to and each disclosure of identified information. The institution must allow the parent or eligible student to inspect this record upon request.

The second part of the definition of an educational record requires that it be "maintained" by an educational agency. If the record is not yet being maintained it is not covered by FERPA. A student grading another student's paper and then calling out the grade and name is not covered because at that point the scores are not being maintained within the meaning of FERPA. Instead, maintain implies that the records are "kept in a filing cabinet in a records room...or on a permanent secure database." Students who handle assignments for a few moments do not maintain the papers as a registrar who keeps records in a permanent file. Without this type of maintenance, information is not covered by FERPA.

Any researcher who seeks to use existing educational records must consider FERPA. Even researchers who are members of the educational institution cannot automatically access student records that contain identifiable information unless they are conducting specific types of studies for or on behalf of educational institutions. If the study does not fall into one of the three categories (test development, student aid programs, improved instruction) then consent is needed in order to view identified files. If the records are de-identified by removal of all designated identifiable information, then FERPA no longer applies. As long as the information sought by the researcher is part of the educational record and the educational institution maintains the record, researchers must follow FERPA and obtain consent.

25 Investigator Responsibilities

25.1 *Investigators*

25.1.1 Principal Investigator

At UCD only **faculty or staff members with University-paid appointments or students/trainees** may serve as the Principal Investigator or as the faculty sponsor on a research project involving human subjects. For research concerning the VA, trainees cannot be the Principal Investigator but may be a co-investigator under the supervision of a sufficiently experienced VA PI.

Adjunct faculty of the University and any investigator whose status is considered to be “in training” (i.e. students, fellows) may serve as a Principal Investigator but they must have a faculty sponsor who will serve as the faculty mentor on the study. If the PI is “in training” then COMIRB requires that the mentor and student sign the Responsibilities of Students/Trainees” document and submit it with their initial application for review. The mentor is also required to review the “Responsibilities of the Mentor” document. By signing the application form both parties agree to take on these responsibilities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet the investigator’s skills or have one or more additional qualified faculty as Co-investigator(s).

25.1.2 Research Team

The PI and other individuals, also known as key personnel, who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol.

25.2 *Investigator Responsibilities*

25.2.1 Compliance with the Approved Protocol

Researchers and research staff must follow the requirements of the research protocol unless the changes to the protocol are prospectively reviewed and approved by the IRB or urgent deviations must be made in the interest of the individual participant then reported to COMIRB as an unanticipated problem.

25.2.2 Investigator Responsibilities Document

The responsibilities of the Principal investigator and the research team are detailed in

the UCD policy entitled “Investigator Responsibilities”. If the PI is required to have a faculty mentor then the mentor also takes on the responsibilities of the investigator described in that document. See “Responsibilities of a mentor” document and “Responsibilities of a student investigator” document for additional details.

25.2.3 Principal Investigator Endorsement and Signature

The Principal Investigator is ultimately responsible for all aspects of the conduct of the research. The PI must be directly involved in certain submissions that require the PI's expert evaluation of risk and benefit (initial submissions, continuing reviews, and unanticipated problem reports). The PI's endorsement of the submission is documented by the PI's electronic stamp within the eRA system created when the PI logs into the system and submits. If a delegate submits on behalf of the PI within the eRA system, the PI is required to sign the PI Attestation form, attesting to his/her responsibilities in making the submission. COMIRB will accept, as a valid PI signature, the eRA electronic system stamp, a wet-ink signature on the attestation form, or a copy of an E-mail from the PI containing an attestation statement.

25.2.4 For Researchers conducting Research following ICH-GCP (E6):

In addition under ICH-GCP (E6), the researcher is responsible to:

- Provide evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB or the regulatory authority.
- Be familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the sponsor.
- Have a qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, responsible for clinical trial-related medical (or dental) decisions.
- Ensure, during and following a participant’s participation in a clinical trial, that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial.
- Ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

25.2.5 For Researchers conducting research under Department of Energy (DOE) requirements:

Researchers are required to follow DOE requirements for the protection of personally identifiable information by completing and complying with the requirements of the “Checklist for IRBs to Use in Verifying that HS Research Protocols Are in Compliance with DOE Requirements”.

25.2.6 For Researchers conducting research under VA

- Investigators and their research staff may only perform those activities in a research study for which they have the relevant credentials and privileges.
- Individuals working under a contract with VA cannot conduct research as VA investigators under a without compensation appointment while simultaneously working as a contractor.

25.3 *Training/Ongoing Education of Principal Investigator and Research Team*

As stated above, one component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. UCD is committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

25.3.1 Orientation

All Responsible Principal Investigators and members of their research team (also known as “key personnel”) must review core training documentation including the “COMIRB Policies for Human Research Protection,” the “Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research “ and the UCD Investigator’s Responsibilities as well as the COMIRB Office web-site. For research personnel who are not listed as “key personnel” on the protocol or protocol application, the PI is responsible for ensuring and documenting education and COI requirements.

25.3.2 Initial Education

The PI and key investigators must complete the COMIRB required CITI Basic Course in the Protection of Human Research Subjects and the CITI HIPAA Course.

All individuals who are engaged in research at the VA, or otherwise subject to VA regulations are required to:

> Complete training in good clinical practice and the ethical principles on which human research is to be conducted before they may participate in human subject research;

Researchers conducting research under Department of Defense regulations requires documented training in human subject research, and the training requirement applies to all members of the study team of a research protocol that will receive Department of Defense funding. This is usually covered by the CITI Basic Course but the research is required to follow the direction of DoD.

25.3.3 Waiver of Initial Education

If investigators or members of their research team can verify that they have successfully completed human subject research training equivalent to that required by the University, they may request a waiver of the requirement for Initial Education from the Director of the COMIRB Office. However, all investigators or members of their research team must complete the requirements of Continuing Education.

25.3.4 Continuing Education and Recertification

All investigators and members of their research teams must meet COMIRB continuing education requirement every three (3) years after certification of Initial Education for as long as they are involved in human subject research. There is no exception to this requirement. Acceptable training includes the CITI Refresher Course or CITI Good Clinical Practices course. Other training may be acceptable. In these cases the researcher should check with the COMIRB Office for a determination.

Investigators who are also COMIRB panel Chair, panel members, or COMIRB Office staff will satisfy the training requirements for panel members and staff as described previously.

Final approval of initial and continuing review submissions will not be granted until the principal investigator and all co-investigators and members of the research team (except for personnel with the role of "Administrator") have completed the initial education requirement (or the continuing education requirement once the initial education requirement has been satisfied).

All individuals who are engaged in research at the VA, or otherwise subject to VA regulations are required to:

- Complete training in good clinical practice and the ethical principles on which human research is to be conducted before they may participate in human subject research;
- Update such training every two years thereafter.

Researchers conducting research under Department of Defense regulations requires documented retraining in human subject research every three years, and the retraining requirement applies to all members of the study team of a research protocol that will receive Department of Defense funding. This requirement is covered by the completion of the CITI refresher course.

For other research personnel, not listed as “key personnel”, the PI is responsible for developing and documenting continuing education and recertification.

25.4 *Department of Defense Requirements*

For research subject to Department of Defense (DoD) requirements, additional training may be required by the DoD Component involved in the research and in compliance with DoD Instruction 3216.02. Investigators are required to provide proof of completed human research ethics and human subjects training to the involved DoD Component (e.g., training certificate, institutional verification of training). The DoD component may evaluate university education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research. Investigators are expected to contact their Program Officer to ensure compliance with the DoD Component training requirements. In the case that the DoD Component’s training requirements exceed those of the University (e.g., in terms of content or frequency of continuing education), investigators are required to complete the additional training and provide proof of completion to the DoD Component.

25.5 *Department of Education Additional Considerations*

All instructional material including teachers’ manuals, films, tapes, or other supplementary instructional material, which will be used in connection with any research or experimental program or project must be available for inspection by the parents or guardians of the children engaged in such research.

25.6 *Additional Resources*

Human research protection information will be made available on the COMIRB Office website on an ongoing basis to ensure that the University research community is apprised of current regulatory and policy requirements and training opportunities.

Newsletters and e-mails alerting investigators to changes in federal guidance, COMIRB policies and procedures or educational opportunities will be sent at least quarterly.

25.7 *Investigator Concerns*

Investigators who have concerns or suggestions regarding UCD human research protection program should convey them to the Institutional Official (Associate Vice Chancellor for Regulatory Compliance), the Vice Chancellor for Research, or other responsible parties (e.g. college dean, departmental Chair) regarding the issue, when appropriate. The Institutional Official will research the issue, and when deemed necessary, convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted.

IRB Chairs and the Director of the COMIRB Office are available to address investigators' questions, concerns and suggestions. There is also the opportunity to provide feedback via the COMIRB Office website.

26 Special Topics

26.1 *Certificate of Confidentiality*

Protection against compelled disclosure of identifiable, sensitive information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d). NIH-funded human subjects research is automatically covered by a Certificate of Confidentiality. Specifically:

NIH policy considers research in which "identifiable, sensitive information" is collected or used, to include:

- Human subjects research as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46), including exempt research except for human subjects research that is determined to be exempt from all or some of the requirements of 45 CFR 46 if the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46); or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

A Certificate may be issued upon application, if such research is not federally funded.

A Certificate prohibits the holder of the Certificate from disclosing, or providing to any other person not connected with the research, the name of research participants or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research. This prohibition of disclosure also applies to any Federal, state, or local civil, criminal, administrative, legislative, or other proceeding. Identifiable, sensitive information under a Certificate shall be immune from the legal process and shall not be admissible as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceeding without the consent of the respective research participant.

Certificates allow disclosure under limited circumstances when it is:

- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

If a Certificate is in place for a study in which consent is obtained from research participants, researchers are expected to inform research participants regarding the Certificate and its protections and limitations in the consent form. If a Certificate is issued after recruitment was initiated, COMIRB does not expect that subjects enrolled prior to issuance of the Certificate be reconsented or re-contacted regarding the Certificate. COMIRB may approve consent documentation which omits mention of the Certificate if the discussion of the Certificate would obfuscate the basic element of consent: a clear statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. Examples include studies posing minimal risk where documentation of consent is waived and a short information sheet or script is used to obtain verbal consent, and studies enrolling in foreign countries where an explanation of an esoteric American regulation would be confusing to foreigners.

The COMIRB may require researchers to apply for a Certificate of Confidentiality for non-federally funded studies. Researchers may consider obtaining a Certificate of Confidentiality for collecting identifiable information such as:

- Information on HIV, AIDS, and other STDs’
- Information on sexual attitudes, preferences, or practices;
- Information on personal use of alcohol, drugs, or other addictive products;
- Information on illegal conduct;
- Information that if released could be damaging to a participant’s financial standing, employability, or reputation within the community;

- Information that might lead to social stigmatization or discrimination if it were disclosed;
- Information on a participant's psychological well-being or mental health;

Researchers may also consider obtaining a Certificate of Confidentiality for genetic studies (including those that collect and store biological samples for future use) and research on behavioral interventions and epidemiologic studies.

26.2 *Mandatory Reporting*

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Colorado State law mandates that certain persons who suspect child or elder abuse or neglect report this to the county department or local law enforcement agency.

UCD policy requires the solicitation of informed consent from all adult research subjects and assent from children involved as research subjects, in addition to the consent of their parents. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of elder abuse or neglect.

The Colorado Child Protection Act, 19-3-304 et seq., requires any physician, surgeon, physician in training, child health associate, medical examiner, coroner, dentist, osteopath, optometrist, chiropractor, chiropodist, podiatrist, registered nurse, licensed practitioner nurse, hospital personnel engaged in the admission, care, or treatment of patients, Christian Science practitioner, school official or employee, social worker, mental health professional, dental hygienist, psychologist, physical therapist, veterinarian, peace officer, pharmacist, victim's advocate, licensed professional counselor, licensed marriage and family therapist, unlicensed psychotherapist, and clergy member who has reasonable cause to know or suspect that a child has been subjected to circumstances or conditions which would reasonably result in abuse or neglect to report or cause a report to be made to the county department or local law enforcement agency.

Colorado's Protective Services For Adults Act, C.R.S. 26-3.1-101 et seq., encourages any physician, surgeon, physicians' assistant, osteopath, physician in training, medical examiner, coroner, registered nurse, licensed practitioner nurse, hospital or nursing home personnel engaged in the admission, care, or treatment of patients, psychologists, mental health professionals, social work practitioners, dentists, law enforcement officials, court-appointed guardians, pharmacists, and employees of a licensed care facility who have observed the mistreatment or self-neglect of an at-risk adult or who have reasonable cause to believe that an at-risk adult has been mistreated to report or cause a report to be made to the county department or local law enforcement agency.

26.3 *Student Research*

26.3.1 Human Subjects Research and Course Projects

Learning how to conduct ethical research is an important part of a student's educational experience. Ethical concerns are much greater when the research activities involve human subjects. At UCD human subjects research protocols are reviewed and approved by the Colorado Multiple Institutional Review Board or the Human Subject Research Committee. However, some research projects assigned for coursework do not meet the definition of human subject research and may not require IRB approval. If there is any question whether a course project meets the definition of human subject research then it

should be submitted to COMIRB for review and assessment in accordance with COMIRB policies and procedures.

Course projects that **DO NOT** require IRB review and approval are limited to projects that do not meet the definition of human subject research. The responsibility for the initial determination as to whether an activity constitutes human subjects research rests with the faculty teacher/advisor/mentor. The faculty teacher should make this determination based on the definitions of “human subject” detailed in section 2.1.2 (DHSS) and 2.1.3 (FDA) of this policy document and “research” detailed in section 2.1.1 of this policy document and the other tools available on the COMIRB website. Since the University will hold them responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the COMIRB Office if there is any uncertainty. Informal requests may be made verbally, by phone contact, by email or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination. Informal requests represent the opinions of COMIRB personnel and are not formal endorsements of the project as Non-human Subject Research.

If the faculty teacher wants COMIRB to make a formal determination that research does not meet the definition of human subject research, this must be submitted formally to COMIRB for its consideration as described in section 8 of this policy document. Classroom projects do not have to be submitted to the IRB for review unless the project meets the definition of human subject research.

It is the responsibility of the faculty teacher, department and school to ensure that all activities conducted in the classroom that involve interaction with the public are conducted in accordance with ethical principles. The IRB is available as a resource to help students develop appropriate class resources but the school is ultimately responsible for their conduct.

The data or data analysis from classroom projects involving human subjects described above **MAY NOT** be presented or published in any form claiming generalizable knowledge.

It is important to keep in mind that any human subjects research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation, contributes to generalizable knowledge and therefore must go through the COMIRB approval process. Capstone projects may or may not contribute to generalizable knowledge and must be considered on a case-by-case basis. Researchers may not present or publish data collected or conduct data analysis without COMIRB approval.

In making a determination of whether or not a class research project requires COMIRB review, the instructor is encouraged to err on the side of caution and to contact the COMIRB office for assistance.

The course instructor is responsible for communicating to the students the ethics of human subject research, for ensuring the protection of human subjects and that a process is in place for obtaining voluntary informed consent from research subjects and for monitoring the students’ progress. Any questions can be directed to the COMIRB office.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the project, and document the determination that the project does not meet the definition of human subject research.

If the project does meet the definition of human subject research, then the project will need to be submitted to COMIRB for review in accordance with COMIRB policies and procedures.

26.3.2 Individual Research Projects Conducted by Students/Trainees

Senior theses, undergraduate research projects, master's and advanced degree research, and similar exercises must be independently submitted for COMIRB review. Trainees (including residents, fellows, post-doctoral trainees, and other non-faculty professionals) must also have a faculty mentor identified on any human subject research project. These students/trainees and mentors must sign the Student/Trainee and Mentor Responsibility agreements, as detailed in section 25.1.1.

26.3.3 Theses and Dissertations

These research activities are considered to meet the federal definition of human subject research and must be independently submitted to the COMIRB by the student-researcher. However, when students conduct research as part of a course of study, a faculty member ultimately is responsible for the protection of the subjects, even if the student is the primary researcher and actually directs the project. Advisors assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course.

Students may not serve as Principal Investigators without a mentor/advisor. They must have a faculty sponsor who fulfills the principal investigator eligibility criteria and who will be responsible for the conduct of the study and serve as faculty mentor on the study.

The mentor/advisor is responsible for ensuring that the student appropriately completes the required documents for submission to the IRB for review. In particular, instructors and students should understand their responsibilities as a principal investigator in accordance with UCD policy.

26.4 *Oral History*

The following is based on guidance received from OHRP:

> "A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution's FWA and HHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under HHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Specifically, for the purposes of this policy, the evaluation of such activities hinges upon whether:

- In order to be subject to the University's human research protections policies, the activity involves a prospective research plan which incorporates data collection, including qualitative data, and data analysis to answer a research question; and
- The activity is designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The activity must meet both of the above standards.

General principles for evaluating Oral History type activities:

1. Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings would NOT constitute "research" as defined by HHS regulations 45 CFR part 46.
   Example: An oral history video recording of interviews with holocaust survivors is created for viewing in the Holocaust Museum. The creation of the video tape does NOT intend to draw conclusions, inform policy, or generalize findings. The sole purpose is to create a historical record of specific personal events and experiences related to the Holocaust and provide a venue for Holocaust survivors to tell their stories.
2. Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) WOULD constitute "research" as defined by HHS regulations at 45 CFR part 46.
   Example: An open ended interview of surviving Gulf War veterans to document their experiences, draw conclusions about their experiences, inform policy, or generalize findings.
3. Oral historians and qualitative investigators may want to create archives for the purpose of providing a resource for others to do research. Since the intent of the archive is to create a repository of information for other investigators to conduct research as defined by 45 CFR 46, the creation of such an archive WOULD constitute research under 45 CFR 46.
   Example: Open ended interviews are conducted with surviving Negro League Baseball players in order to create an archive for future research. The creation of such an archive would constitute research under 45 CFR 46 since the intent is to collect data for future research.

Investigators are advised to consult with the COMIRB Office regarding whether their oral history project requires COMIRB review.

26.5 *Research Involving Coded Private Information or Biological Specimens*

Any studies involving collection and / or storage of biological specimens must be submitted to COMIRB.

UCD and Affiliate policy is based on the OHRP guidance document entitled, **"Guidance on Research Involving Coded Private Information or Biological Specimens"** (October 16, 2008, http://www.hhs.gov/ohrp/policy/cdebiol.html). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR 46).
- Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subject research.
- Provides guidance on who should determine whether human subjects are involved in research.

For purposes of this policy, coded means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the

individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human subject, obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. "Obtaining" means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do not involve human subjects if the following conditions are both met:

(1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; **and**
(2) The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    (a) The key to decipher the code is destroyed before the research begins;
    (b) The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (coded information agreement). A template for such an agreement is available on the COMIRB website.
    (c) There are COMIRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
    (d) There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

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

26.5.1 Who Should Determine Whether Private Coded Information of Specimens Constitutes Human Subjects Research

The investigator, in consultation with the panel Chair, Expedited/Exempt Manger or Director of the COMIRB Office, will determine if the research involving coded information

or specimens requires COMIRB review. If the request is by email or writing, it is the investigator's responsibility to maintain documentation of this non-official recommendation. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and an official COMIRB determination letter/email will be kept on file.

26.6 *Banking of Human Biological Specimens Collected from Veterans for Research Purposes*

26.6.1 VA Policy

It is the policy of ECHCS to comply with VHA Directive 2000-043 "Banking of Human Subject's Specimens" and the March 28, 2001 memorandum from the Chief Research and Development Officer (CRADO) entitled VHA Directive 2000- 043 "Banking of Human Subjects' Specimens".

The following describes the procedures required for the collection and banking of human biological specimens and related clinical data collected from veterans/subjects for research purposes.

26.6.2 VA Definitions

Human biological specimen (HBS): any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic, or surgical procedures.

"Stored" Specimen: specimens collected only for the purposes stated in the current protocol, and which will be destroyed at the completion of this study. These specimens are not considered banked specimens.

"Banked" Specimen: specimens collected and stored for future research purposes are considered "banked" specimens.

On-site tissue bank: a tissue repository or storage facility established in a VA facility by a VA-paid investigator. It contains human biological specimens collected under VA-approved research protocols that are under both VA ownership and VA control.

VA-approved off-site tissue bank: an approved tissue bank located at a non-VA facility and has the appropriate approval from the Chief Research & Development Officer (CRADO) at the VA Central Office. Off-site tissue banks are approved on a per protocol basis, with the exception of some National Cancer Institute (NCI) - sponsored tissue banks. (See Attachment C for the VA Central Office's "FAQ: Banking of Human Biological Specimens for Research" for more information and a list). Non-VA sites that may not be acceptable include non-academic, for-profit institutions, such as pharmaceutical companies.

26.6.3 VA Investigator Responsibilities

1. The VA Investigator is responsible for:
    a) Obtaining full approval of the protocol and consent form from the appropriate committees prior to the initiation of the study.
    b) The VA Investigator will ensure that the research is conducted according to federal regulations, state law, and VHA policies.

c) The VA Investigator must obtain a Waiver from VA Office of Research and Development (ORD) before banking human biological specimens outside of the VA.
d) The VA Investigator will maintain a copy of the signed consent form under which the specimen was collected.
e) The VA Investigator will maintain a record for a minimum of 10 years describing the use/disposition of each specimen and the protocols under which the specimens are used, as well as the IRB approval of the protocol.
f) If the specimens are sent outside the ECHCS for the analyses as described in the protocol, the VA Investigator assures that the specimens will be used for the approved purposes only, the specimens will be stored off-site for no more than five years and that upon completion of use of the specimens, the VA Investigator assures that they will be destroyed by the institution or returned to the ECHCS for storage or destruction.
g) For the banking of specimens for future research use, the VA Investigator must assure that these specimens will be banked in a VA-approved tissue bank. If the proposed tissue bank is not currently VA-approved, the VA-Investigator will not start the study until the proposed tissue bank has been approved by the VA Central Office.
h) For the banking of specimens for future research use, the VA Investigator assures that the reuse of these specimens will be consistent with the consent under which they were collected, and the re-use will only occur through a VA-approved protocol.

2. The VA Research Office will maintain the records for all new and existing banks, both VA-approved off-site tissue banks and on-site tissue banks within the ECHCS.
3. The COMIRB is responsible for reviewing the protocol and ensuring that all elements are addressed in the consent form and in compliance with the required regulations.
4. The R&D Committee is responsible for ensuring that the research protocol complies with all regulatory guidelines.

26.6.4 VA Procedures

1. The PI will prepare and submit an Application for an Off-Site Tissue Banking Waiver (VA Form 10-0436) and required documentation, which can be found on the VA Office of Research & Development (ORD) website.
2. A tissue bank established at a VA site by a VA-paid investigator does not require approval from ORD. The VA Research Office should maintain records of all tissue banks within the facility.
3. A researcher must obtain a waiver from ORD before banking human biological specimens outside of the VA. In general, an off-site tissue bank must be approved for each protocol.
4. The informed consent under which the specimen was collected must meet all the requirements in Appendix C of VHA Directive 1200.05 “Requirements for the Protection of Human Subjects in Research.” In addition, the informed consent must clearly address the following:
    - The types of specimens that will be stored and the name and location of the biorepository/tissue bank where they will be stored.
    - The types of future research that the sample will be used for.
    - If the specimen will be shared with other researchers for approved research protocols.

- The length of time the specimen will be stored.
- If the specimen will be labeled with a code that doesn't contain any personal identifiers (i.e., protected health information as defined by HIPAA) and if the subject's clinical data will be linked to the specimen.
- When and under what conditions research results will be conveyed to the subject, the subject's family, or the subject's physician.
- Note: Laboratories that test human specimens cannot report patient specific results for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of individual patients unless the laboratory is Clinical Laboratory Improvement Amendments of 1988 (CLIA) certified.
- The steps necessary for the subject to withdraw from the study and any future studies in which the specimens may be used. The consent must indicate what will occur to the data collected to that point and that the specimen and the code that links the subject's clinical data to the specimen will be destroyed.
- Disclose any potential commercial benefits and if the subject will receive money or other benefits.
- Disclose any intent to perform genetic tests.
- Disclose any potential risks to the subject or the subject's family. Potential risks may include breach of confidentiality, which may lead to discrimination in the areas of employment, insurability, social stigmatization, or psychological stress caused by disclosure of adverse information to the subject or the subject's family.

26.7 *Community-Based Research*

Research within the community can take multiple forms and have varying degrees of community involvement. At one end of the continuum, research may simply occur in a community; at the other end, the community is the moving force behind the research, developing the research agenda and participating in the development of the research design and collection and analysis of data. In some community-based research community members wear two hats – they may obtain informed consent from subjects or collect or analyze identifiable data, as well as being individual research subjects. Principles of beneficence and justice require that PIs be cognizant of the potential effects of research on individuals well as the communities in which the research is conducted to avoid harm to a community. In some cases PIs must assure that there is a process for obtaining community consent for research.

26.7.1 Considerations for Review of Community-Based Research

In addition to the Criteria for IRB Approval of Research set forth in Section 13, the COMIRB will consider:

- The degree of community involvement in research and who speaks for the community.
- Whether community organizations are engaged in research under the regulations as described in Section 10.
- Human subjects protection training for community members.
- Protection of data in community-based research.
- Review procedures to accommodate the dynamic nature and process of community-based research.
- Plans for dissemination of results of research to the community.

26.7.2 Degree of Community Involvement and Who Speaks for the Community

Not all research is community-based participatory research (CBPR), which is typically an equal collaboration of community and researchers. The COMIRB will look to the researcher to describe the degree and nature of community involvement in the research and to describe processes for community involvement in and agreement to participate in the research. The PI is expected to be sensitive to who speaks for the community and to describe appropriate processes for community input and agreement to participate in the research study. Documentation from community advisors or committees may be an appropriate way to demonstrate the agreement and scope of community involvement in the study. COMIRB may also request that the research team utilizes the CCTSI Community Engagement Consultation Service.

26.7.3 Community Organizations Engaged in Research

Community organizations that have a legal status (corporations, 501(c)(3) organizations, LLCs) and that are engaged in research must obtain an FWA and either have their own IRB review the proposed research or request that the COMIRB act as the IRB of record for the community organization and enter into an IRB Authorization Agreement with the COMIRB. Community organizations are engaged in research if:

- The community organization receives an award through a grant, contract or cooperative agreement.
- Employees or agents from the community organization perform invasive or non- invasive procedures.
- Employees or agents from the community organization intervene for research purposes with a subject of the research by manipulating the environment.
- Employees or agents from the community organization interact for research purposes with any subject of the research (such as administering surveys, conducting interviews).
- Employees or agents from the community organization obtain the informed consent of human subjects.
- Employees or agents from the community organization obtain for non-exempt research purposes obtain identifiable information or identifiable biological specimens from any source. This activity can include observing or recording private behavior, using, studying or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

The PI and the community organization that needs an FWA are encouraged to discuss with COMIRB staff how to obtain an FWA

26.7.4 Human Subject Protection Training for Community Members

Community organizations that obtain an FWA must have their principal investigator complete the COMIRB required CITI Basic Course in the Protection of Human Research Subjects and the CITI HIPAA Course.

Community members who perform invasive or non-invasive procedures, intervene for research purposes with a subject of the research by manipulating the environment, interact for research purposes with any subject of the research (such as administering surveys, conducting interviews), obtain the informed consent of human subjects, or obtain for non-exempt research purposes obtain identifiable information or identifiable biological specimens from any source, must complete the COMIRB-required CITI Basic Course in the Protection of Human Research Subjects and the CITI HIPAA Course, or be trained in these principles by the PI and research team. The PI should present a

training plan for the inclusion of community members as researchers and should describe how the PI will manage and monitor the activities of community members who act as both researchers and subjects.

26.7.5 Protection of Data in Community-Based Research.

The PI is expected to develop a plan for the protection of identifiable data that assures that community members who are also acting as researchers understand their responsibilities when collecting or analyzing identifiable data.

The PI and the community may have conflicting views of the dissemination of the results of community-based studies. The PI should describe how the entire research team, including the community, will share responsibility for deciding what and when results developed in the study will be disseminated. The PI is encouraged to consider forming a committee of researchers and community members to collaborate on the protection of data and the dissemination of study findings.

26.7.6 Review Procedures to Accommodate the Dynamic Nature of Community-Based Research.

The COMIRB appreciates that community-based research is dynamic and that the scope and form of the research may not be evident early in the process. Indeed, community-based participatory research is supposed to be fluid and iterative.

It may be useful for researchers to plan their community-based studies in phases. Some activities, such as formative interviews and meetings with community representatives may be preparatory to research because they are not yet based on a research question. These activities may not constitute research under the regulations because they are not designed to develop or contribute to generalizable knowledge, and therefore may not need IRB review at this stage. Once researchers and the community develop a research question and plan for conducting the research, they may still decide to seek approval in phases to accommodate research designs that build on findings of previous activities (for example, using results of a survey to create and test an intervention).

The COMIRB recognizes that some funding agencies require IRB approval as a condition of funding, even if the initial activities are non-human subject research or preparatory to research. In such cases, it may be possible to conduct phased reviews. PI and community members are encouraged to discuss their plans with COMIRB staff to address the timing and scope of review.

26.7.7 Dissemination of Results.

The guiding principle in the ethical selection of research subject groups is that risks of the research should fall upon the groups who might benefit from it. Publication in scholarly journals alone may not be a sufficient vehicle to share results of research with the community. PI should include a plan for disseminating the results of community-based research using methods appropriate to the community, which may include using community members to help disseminate results.

26.8 Marijuana Research

When a study is submitted to COMIRB for review, the study will be flagged in InfoEd on the summary page under legacy variables. Senior IRB staff will consult with UCD legal to confirm

that the study meets the definition of permissible research and that legal considerations have been addressed. Legal counsel must provide prospective approval (prior to COMIRB review and approval) for research that involves bringing marijuana on campus that has not been properly obtained from the FDA and marijuana research that involves providing marijuana to human subjects, subsidizing the purchase of marijuana or studying the first-person effect of marijuana on human subjects that do not have an IND or are approved by the FDA.