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I. GENERAL ADMINISTRATION

A. INTRODUCTION

1. Purpose of Standard Operating Procedures

The purpose of these Standard Operating Procedures (SOPs) is to:

- State the institutional authority under which the UCHealth Institutional Review Board (IRB) is established and empowered
- Define the purpose of the IRB
- State the principles governing the IRB to ensure that the rights and welfare of research participants are protected
- State the authority of the IRB
- Define the scope of the IRB
- Define the relationship of the IRB to other committees and to officials within the University system

Policies, guidance, procedures and information related to the conduct of research are presented in this document as a resource and guide to educate UCHealth IRB members on the issues governing human subjects' research. The IRB office may be contacted at 970.237.7970 for information or additional copies of this document.

These SOPs govern research activities at each member organization hospital of UCHealth where research is conducted except for UCHealth Denver Metro sites, which shall be governed by the policies and procedures of the Colorado Multiple Institutional Review Board (COMIRB). For the avoidance of doubt, in any case where research is conducted at University of Colorado Hospital or any of its outpatient facilities, or any UCHealth Denver Metro sites, the terms of these SOPs do not apply.

2. Mission

a. *UCHealth's Vision, Mission and Values*

Vision: From health care to health.

Mission: We improve lives. In big ways through learning, healing and discovery. In small, personal ways through human connection. But in all ways, we improve lives.

Values: Patients first, Integrity, Excellence

b. *IRB Mission Statement*

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The UCHealth IRB believes in protecting the rights of research subjects and reducing their risk of participation. Through education, communication, and standardized processes, members of the IRB and the clinical research team work together to form a research protection umbrella for UCHealth patients and research subjects. This umbrella is truly a "research protection program" that ensures ethical and innovative research for our patients, subjects and employees of UCHealth.

3. Use of SOPs

The UCHealth IRB must maintain and follow all written policies and procedures consistent with federal regulations, good clinical practice, and research ethics when reviewing proposed research.

4. Maintenance of SOPs

The UCHealth IRB is committed to maintaining and following up-to-date policies and procedures that adhere to regulatory mandates and ethical principles. Following federal regulations and guidance supported by institutional policies assures that the rights and welfare of the human participants of such research will be overseen and protected in a uniform manner, regardless of changes in personnel. Written procedures must be in place to ensure the highest quality and integrity of the review and oversight of research involving human participants and for the adequate documentation of such oversight.

New or revised SOPs may be required upon changes to regulations, federal guidelines, or research practices, as well as changes to UCHealth policies. The SOPs will be reviewed at least every three years, or more frequently as needed, by the Institutional Official (IO) and any appropriate IRB staff. New or revised policies, procedures, and guidance documents will be reviewed by legal counsel and approved by the IO and will be disseminated to appropriate individuals and departments. Obsolete versions of the IRB SOP will be maintained in the IRB office. Members of the IRB and IRB staff will receive training on any new or revised policies and procedures. Each new IRB member or staff employee must review all applicable SOPs prior to undertaking any responsibilities for the IRB.

Forms, including checklists and worksheets, are to be used to ensure that policies are integrated into the daily operations of research and review and to assist IRB staff and IRB members in the review process. Forms are either controlled or uncontrolled. Controlled forms are regulatory documents that become part of the permanent record of IRB review. Uncontrolled forms are management tools designed to assist with the IRB review process and do not become a formal part of the IRB submission. Final versions of controlled forms will be uploaded to IRBManager and/or maintained in a paper file.

REFERENCES

45 C.F.R. § 46.108(a)(3) & ()

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21 C.F.R. § 56.108

21 C.F.R. § 56.115(6)

B. Institutional Authority Under Which the IRB Is Established and Empowered

The UCHealth IRB is established and empowered under the authority of the UCHealth Board of Directors. UCHealth requires that all research projects that meet the definition of human subjects research be reviewed and approved by the UCHealth IRB prior to initiating any research-related activities.

C. Purpose of the UCHealth IRB

The purpose of the UCHealth IRB is to ensure that the rights and welfare of human subjects are protected in all medical, behavioral, and social sciences research. The IRB reviews and oversees such research to ensure that it meets the ethical principles and that it complies with federal regulations that pertain to human subject protection and other pertinent regulations and guidelines.

In accordance with federal and state regulation governing research, an IRB must review and approve research involving human subjects prior to its initiation. It is the responsibility of the IRB to determine whether proposed research exposes subjects to unreasonable or unnecessary risk, to review informed consent forms and ensure compliance with ethical consent processes, and to monitor the progress of research. In its deliberations, the IRB will use the ethical principles, as detailed in the Belmont Report (1979), to make its determination.

References:

45 C.F.R. Part 46

21 C.F.R. Part 50

21 C.F.R. Part 56

D. The Ethical Principles that Govern the IRB

Three basic principles are particularly relevant to the ethics of research involving human subjects as suggested in the Belmont Report.

- Respect for Persons
- Beneficence
- Justice

Respect for persons incorporates at least two ethical convictions. First, individuals should be treated as autonomous agents. Second, people with diminished autonomy are entitled

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to protection. Respect for persons demands that subjects enter into the research voluntarily and with adequate information to make their decision.

Beneficence means that persons must be treated in an ethical manner not only respecting their decision and protecting them from harm, but also by making efforts to secure their well-being.is often understood as acts of kindness or charity, but in research it is understood in a stronger sense, as an obligation. Persons will be treated Two general rules have been formulated as complementary expressions of beneficent actions:

- Do no harm
- Maximize possible benefits and minimize possible harms

The definition of justice has long been associated with social practices of punishment, taxation and political representation. The research principles of justice outline the moral requirements that include fairness in selection procedures and outcomes. Injustice may arise if overall distribution of the burdens and benefits of research are not distributed fairly throughout all populations no matter their race, gender, age, or socioeconomic level.

1. Application of Principles to IRB Approval Requirements

Application of these general principles of research leads to consideration of the following approval requirements:

- Informed Consent
    - Information—what a reasonable “volunteer” would want to know
    - Knowledge of reasonably foreseeable consequences or risks
    - Knowledge of alternate treatments or therapies
    - Comprehension—with special provisions when comprehension is limited
    - Voluntariness—free of coercion and pressure
- Assessment of Risk and Benefit
    - Risks to subjects are justified.
    - Risks should be reduced to only those necessary to achieve the objective.
    - Whenever appropriate, procedures will be used that are already being performed on the subject for diagnostic or treatment purposes.
    - Only those risks and benefits of therapies related to the research will be considered.
- Selection of Subjects

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- The appropriateness of the recruitment plan and safety precautions surrounding risk minimization for vulnerable subjects must be demonstrated.
- Potentially beneficial research should not be limited to a select few or a convenience sampling.

REFERENCES

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research (1979), https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

E. AUTHORITY OF THE UCHEALTH IRB

1. Scope of Authority

The IRB exists to review biomedical and behavioral research involving human subjects regardless of the source of funding and location of the study. All human research projects within UCHealth entities (excluding UCHealth Metro Denver entities, including but not limited to University of Colorado Hospital and Highlands Ranch Hospital) that are initiated or completed by members of its workforce or affiliated medical staff and do not include University of Colorado Denver (CU) School of Medicine employed faculty on the research team, must be reviewed and approved by the IRB before the research may begin. This policy applies to research projects that involve physicians or employees such as nurses, pharmacists, and allied health personnel performing patient procedures, interviewing, or collecting data that are included in the design of the research project. Examples of research procedures that are subject to IRB approval may include: administering medications, drawing blood, collecting biologic samples or applying diagnostic techniques such as x-rays or scans, interviewing patients, or disclosing of patient information as part of a research project.

2. Authority to Approve, Disprove, or Modify Studies

All research activity that takes place at UCHealth and its entities must have IRB approval and UCHealth facility approval. This includes but is not limited to: clinical trials, behavioral and qualitative research, records or chart review, subject selection and recruitment, diagnostic testing evaluation, surveys, and use of pathological specimens or discarded tissue for research. Quality improvement projects that include publication may require IRB approval. Exempt research projects require submission to the IRB for determination of exempt status.

All research involving human subjects regardless of sponsorship must comply with the informed consent procedures. Certain categories of research may have the informed consent requirement waived. See Section VIII.C (“Exemptions and Waivers of Written Informed Consent”) for more information.

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Once the researcher has submitted an application and received IRB approval, he/she must abide by the guidelines established by the Common Rule and the Belmont Report.

The IRB has the authority to ensure that research is designed and conducted in such a manner that it protects the rights and welfare of participating subjects. It also has the authority to not only approve research but require modifications or disapprove research activities that fall within its jurisdiction.

3. Authority to Require Progress Reports From Investigators and Oversee Conduct of the Study

The IRB has the authority to conduct continuing review as required to protect the rights and welfare of research subjects. This includes requiring progress reports, auditing the conduct of the study, and observing the informed consent process of any study under its jurisdiction.

4. Authority to Suspend or Terminate Approval

The IRB may suspend or terminate approval of a study and/or place restrictions on a study if that study is determined to be conducted outside the regulations that govern research or, more importantly, if it could cause unnecessary risk or harm to subjects.

5. Assurance of Independence

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by institutional officials or other committees. However, those officials or committees may not approve research if it has been disapproved by an IRB. If review by other officials or committees is required, then the principal investigator (PI) and research team may not begin research until review is complete.

The IRB has the mandate to act as an independent entity within the corporate structure of UCHealth. The actions of the IRB, its Chairperson, members, and administrative staff derive their authority in matters of human subject protection from the federal regulations. The IRB is a separate and distinct authority from UCHealth.

It is the responsibility of the Institutional Signatory Official to maintain and enforce the independent nature of the relationship between the IRB and UCHealth. The Institutional Signatory Official for the IRB is the IO, whose responsibilities include receiving reports, granting authority to respond, and describing the types of responses to attempts to inappropriately influence the IRB.

REFERENCES

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research (1979), https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf

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Federal Policy for the Protection of Human Subjects (the "Common Rule"), codified at 45 C.F.R. Part 46

45 C.F.R. § 46.104

45 C.F.R. § 46.101 (i)

F. FEDERAL WIDE ASSURANCE

The institution has a Federal Wide Assurance (FWA) which guarantees to the Department of Health and Human Services (HHS) that they will follow procedures to assure the protection of all human subjects involved in research projects. The FWA is a formal agreement between the Office for Human Research Protections (OHRP) and UCHealth that is signed by the IO. This FWA applies to all research involving human subjects regardless of source of funding or support conducted at UCHealth. Research conducted elsewhere by physicians, students, staff or other representatives of UCHealth in connection with their institutional responsibilities must adhere to these guidelines as well. A copy of the FWA (FWA No. FWA00023003) is available in the IRB office and also online at http://ohrp.cit.nih.gov/search/search.aspx?styp=bsc.

II. IRB ORGANIZATION & RELATIONSHIPS

A. IRB FUNCTIONS

The IRB derives its authority from the UCHealth Board of Directors and, as such, has a duty to comply with all UCHealth policies, including, for example, any policy related to institutional conflicts of interest, and is further subject to the oversight of the IO, except that the IO may not in any case approve research that has been disapproved (or not yet approved) by the IRB.

The IRB is responsible for the following:

- Conducting initial and continuing review of research;
- Reporting findings and actions to the investigator and the institution;
- Determining which projects require review more often than annually;
- Determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;
- Ensuring prompt reporting to the IRB of proposed changes in a research activity, and ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects;
- Ensuring prompt reporting to the IRB, the IO, and other appropriate institutional officials, any department or agency head and OHRP for research conducted or

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supported by HHS, and the Food and Drug Administration (FDA) for FDA-regulated research of:

- Any unanticipated problems involving risks to human subjects or others;
- Any instance of serious or continuing noncompliance with the applicable HHS and FDA regulations or the requirements or determinations of the IRB;
- Any suspension or termination of IRB approval.

The IRB Department supports the IRB in these functions. The IRB department is the administrative support for the UCHealth IRB. The IRB department reports to the IO. All communications (letters, responses, etc.) that go to state or federal agencies related to human subjects research and the IRB must be approved by the IO prior to submission.

REFERENCES

45 C.F.R. § 46.108

21 C.F.R. § 56.108

B. OVERSIGHT RESPONSIBILITIES – INSTITUTIONAL OFFICIAL

The IO is the UCHealth Chief Clinical Research Officer and reports to the University of Colorado Hospital (UCH) Chief Medical Officer. The UCHealth Board of Directors and CEO have appointed the Chief Clinical Research Officer to assume this role. The IO has the ultimate responsibility for the oversight of research and IRB function. The IO is an official of the institution who has the knowledge and legal authority to act and speak for the institution and effectively fulfill the research oversight function. The IO ensures the protection of the rights and welfare of research subjects and the institution itself within the area of research. The rights and welfare of human subjects must always take precedence over the needs of science or fiscal considerations.

It is the IO's responsibility to sign and oversee the conditions of the FWA. It is also his or her responsibility to commit the resources needed by the IRB to establish and maintain the Research Protection Program for the Health system.

The IO is ultimately responsible for all regulatory and compliance issues related to human subjects research and the IRB, except for those issues explicitly reserved for determination by the IRB. Should allegations of noncompliance arise, the IRB must notify the IO immediately and assist the IO with the investigation and determination of subsequent disciplinary action of medical staff as required.

The IO is responsible for:

- Promoting effective institution-wide communication and guidance on human subjects research;

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- Serving as a knowledgeable point of contact for OHRP and other federal agencies, or delegating this responsibility to another appropriate individual;
- Establishing administrative arrangements to promote effective and proper IRB functions and operations in compliance with IRB SOPs.
- Establishing personnel requirements for the IRB;
- Appointing the IRB Chairperson and Vice Chairperson positions;
- Evaluating the ongoing performance of the IRB Chairperson and Vice Chairperson;
- Guiding the IRB and Research Administration offices in establishing the Research Protection Program at UCHealth;
- Supervising any delegation of the IO's responsibility to provide oversight of IRB functions; and
- Assisting in the ongoing performance evaluation of IRB Members.

An IO cannot approve research that has been disapproved (or not yet approved) by the IRB.

REFERENCES

45 C.F.R. § 46.112

21 C.F.R. § 56.112

C. IRB INSTITUTIONAL REPORTING STRUCTURE

The IRB receives its authority from the IO and is a distinct institutional body charged with research protection and compliance. There is a direct relationship between the IRB membership and staff and the IO, who reports to the UCH Chief Medical Officer.

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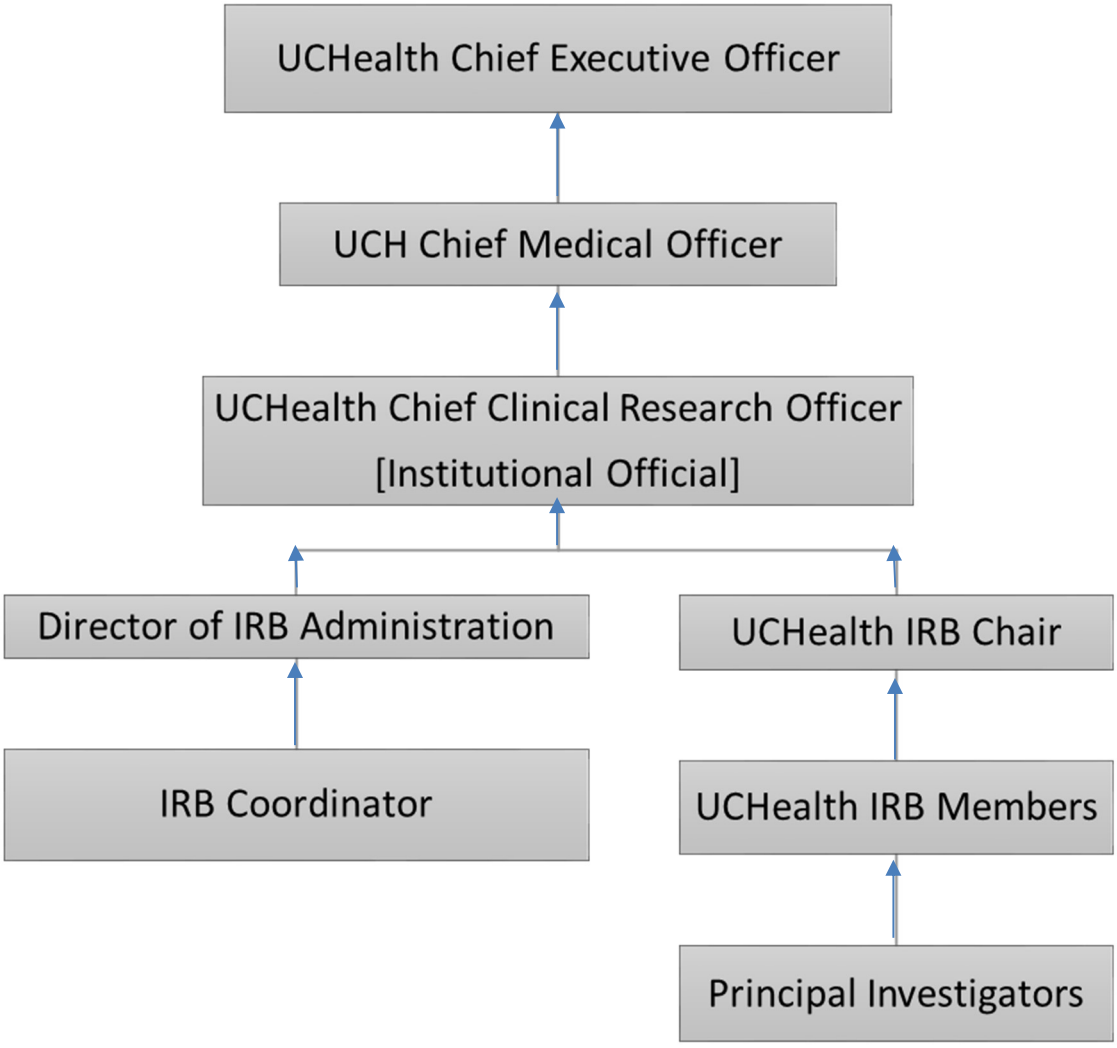

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D. SIGNATORY AUTHORITY

The Institutional Signatory Official for the IRB is the IO. The Institutional Signatory Official is authorized to sign documents in connection with the review and approval of research projects involving the use of human subjects that have been reviewed and approved pursuant to UCHealth policies and procedures upon the decision of UCHealth IRB.

The Institutional Signatory Official may authorize others to sign documents. Such authorization must be made in writing. In all cases, individuals must sign their own name and no other, and indicate their title under their signature.

The results of reviews and actions taken by the IRB that grant Investigators initial or continuing approval of research or approval, acknowledgement, or acceptance of any other revisions or reports may be signed by any designated member of the IRB staff. The results of reviews and actions taken by the convened IRB that result in disapproval may be signed by the Institutional Signatory Official. Communications regarding determinations of serious or continuing noncompliance or unanticipated problems will be signed by the Institutional Signatory Official or his or her designee.

Routine internal correspondence that does not imply or appear to imply approval of research protocols may be signed by an IRB staff member.

Official letters or memoranda sent to agencies of the federal government, funding agencies (either private or public), or their agents will be signed by the Institutional Signatory Official.

Any letters, memoranda, or emails sent representing the decision or opinions of the Chair of the IRB or his or her designee may be signed by a designated member of the IRB staff, as long as the correspondence does not imply review and approval of research. The IRB staff member who is designated to send such correspondence must be so authorized by the IRB Chair or an IRB majority at a convened meeting.

REFERENCES

45 C.F.R. § 46.108(d)(4)

45 C.F.R. § 46.115(a)(6)

21 C.F.R. § 56.108(b)

21 C.F.R. § 56.115(a)(6)

E. INVESTIGATORS

Investigators bear the primary responsibility for ensuring that research protocols meet the standards established by both federal and state regulations and the IRB. Compliance with these regulations helps to ensure the protection of human subjects and the integrity of UCHealth as a research institution.

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An investigator is a licensed health care provider or practitioner or other UCHealth employee or student qualified to conduct investigational studies with human subjects within his or her own field of expertise. Investigators may not conduct research at UCHealth without obtaining prior approval to do so from an IRB and must comply with the requirements, directives, and policies of the IRB. The IRB shall require and share records and documents as necessary with investigators for the protection and safety of subjects who are involved in research projects.

Research that involves UCHealth patients must be conducted by UCHealth-affiliated physicians, RNs, and/or allied health personnel. If the researcher is not a member of the UCHealth medical staff or an employee, a physician champion or employee must be included as sub-investigator.

Researchers outside of UCHealth must apply for and receive approval from an IRB and contact Research Administration for facility review prior to initiation of their research. Physicians conducting research in their own private facilities, without involvement of UCHealth staff or patients, are not considered to be under the jurisdiction of this policy.

F. Relationship with Regulatory Agencies

The IRB shall make all records available for inspection to authorized FDA and/or OHRP investigators and agents whenever such request is made. As appropriate, severe adverse events, deaths, and unanticipated consequences resulting from regulated research shall be reported to the FDA and/or OHRP and any non-compliance on the part of any investigator shall be documented and reported. All communications (letters, responses, etc.) that go to state or federal agencies related to human subjects research and the IRB must be approved by the IO prior to submission.

III. ACTIVITIES REQUIRING IRB REVIEW

A. Human Research

Before a research project involving human subjects is initiated, it must first be reviewed and approved by the IRB. Consequently, research will be conducted according to the federal and state regulations governing research. Approval is required for all research involving human subjects, including but not limited to drug studies, diagnostic studies (invasive or non-invasive), in vitro studies using clinical specimens, collection of discarded tissue, retrospective or prospective chart review, certain quality assurance activities, surveys, and behavioral studies regardless of whether or not research is funded by an outside agency.

No intervention or interaction with human participants in research, including recruitment, may begin until the IRB has reviewed and approved the research protocol. “Human subjects research” is any activity that either:

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(1) meets the HHS definition of "research" involving "human subjects" as defined in the HHS regulations, or

(2) meets the FDA definition of "clinical investigation" that involves "human subjects" as defined in the FDA regulations.

The boundary between research and innovative care is a complex and controversial issue. However, for the purposes of this IRB, human subjects research is defined as any activity which has the intent of securing information from humans for the purpose of advancing generalizable knowledge. Research is considered to involve "human subjects" when an investigator 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 about a living individual. Such activity may or may not differ in a significant way from customary medical or other professional practice. For purposes of these SOPs, the terms "research," "clinical research," "clinical study," "protocol," "study," "investigation," and "clinical investigation" are considered synonymous.

B. ACTIVITIES THAT REQUIRE IRB APPROVAL

Activities that require IRB approval include, but are not limited to, the following:

1. Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the Food Drug & Cosmetics Act (FDCA), or need not meet the requirements for prior submission to the FDA under the same sections of the FDCA, 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;
2. Collection and use of data about a series of standard procedures or treatments for dissemination or generalization if the activity meets the definition of "human subjects research";
3. Patient care or the assignment of normal participants to any intervention that is altered for research purposes in any way;
4. A diagnostic procedure for research purposes that is added to a standard treatment;
5. "Systematic investigations" involving innovative procedures or treatments. For example, if an investigator plans to collect information about an innovative procedure for scientific purposes or will repeat the innovation with other participants in order to compare it to the accepted standard;
6. Emergency use of an investigational drug or device (See Section VII.A for additional information.);

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7. Treatment use requests, where prospectively planned, non-emergency medicine research involves the use of an investigational agent under a treatment investigational new drug (IND) (a.k.a. a single patient IND), expanded access treatment investigational new drug application (IND) or treatment investigational device exemption (IDE) for an individual patient;
8. Emergency medicine research that is prospectively planned using investigational drugs, devices, or biologics requires IRB approval. If the researcher intends to waive the requirement for informed consent, then additional requirements must be met, including community consultation and public disclosure;
9. Data, human cell, or tissue repositories that collect, store and distribute human tissue materials (including genetic tissue) for research purposes;
10. Investigator-initiated research—An investigator who both initiates and conducts, alone or with others, a research project or clinical trial, regardless of the source of funding or support;
11. Student research—Directed or independent human subjects research projects which employ systematic data collection with the intent to contribute to generalizable knowledge, including (a) all masters' theses and doctoral dissertations that involve research with human subjects, and (b) all projects that involve research with human subjects and for which findings may be published or otherwise disseminated;
12. Access to protected health information (PHI)—Investigators conducting research with PHI maintained within any of the covered entities of UCHealth must provide the IRB with appropriate information to obtain approval of the activity prior to access of the PHI; and
13. Collaborative research requires IRB review by each performance site unless an IRB authorization or independent investigator agreement is in place or carried out under the terms of a cooperative agreement.

C. ACTIVITIES THAT DO NOT REQUIRE IRB APPROVAL

Proposals for projects that do not qualify as human subjects research may not require IRB review. Additionally, activities such as quality assurance or quality control, program and fiscal audits, and certain disease monitoring as prescribed by the Public Health Department generally do not qualify as research, but may require review to determine that review is not necessary, or that a privacy board determination is required.

A single retrospective case report is a medical/educational activity and does not meet the Federal Policy for the Protection of Human Subjects definition of "research." In general, review of medical records for publication of case reports of three or fewer patients is not considered human subjects research and does not require IRB review and approval. Under HIPAA, a single case report is an activity to develop information to be shared for

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medical/educational purposes. Therefore, the use of PHI to prepare a paper for publication of a single case report does not require IRB review for HIPAA purposes. If the data are de-identified, no waiver or authorization is required. If, however, the investigator wishes to publish data with HIPAA identifiers, an authorization signed by the patient is required.

Investigators have the option to obtain documentation from the IRB that the activity is not subject to IRB review.

D. FAILURE TO SUBMIT A PROJECT FOR IRB REVIEW

There are significant implications for engaging in activities without IRB approval. To do so is in violation of institutional policy. This action may result in reprimand, loss of privilege and/or disciplinary action for the researcher. Data and results from such studies may not be used or published unless IRB approval had been obtained prior to collecting the data.

REFERENCES

Federal Wide Assurance

45 C.F.R. § 46.102(l) & (e)

21 C.F.R. § 50.3(d)(g)

21 C.F.R. § 56.108(b)(1)

45 C.F.R. § 46.108(a)(3)

21 C.F.R. § 50.24

OPRR Reports, Emergency Medical Care, May 15, 1991

OPRR Reports, Informed Consent Requirements in Emergency Research, October 31, 1996

OHRP Guidance Research Involving Coded Private Information or Biological Specimens, Oct. 16, 2008

OHRP Issues to consider in the research use of stored data or tissues, Nov. 7, 1997

OHRP Guidance, Engagement of Institutions in Research, Oct. 16, 2008; FDA Guidance on Single Patient IND, Feb. 4, 2015.

FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors, Exception from Informed Consent Requirements for Emergency Research, April 2013

IV. MEMBERSHIP

A. MEMBERSHIP OF THE IRB

1. Number of Board Members

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The UCHealth IRB will consist of no less than eight persons to serve as regular, voting members of the IRB.

2. Member Selection Criteria

The appointed members shall reflect various backgrounds of experience and expertise. They should be professionally competent to review specific aspects of research procedures and study designs with the primary objective of safeguarding the rights and welfare of human subjects. The appointed members must also be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

Qualified persons from multiple professions will be considered for membership. IRB membership will not consist of only men or only women. The institution will make every effort to have a diverse membership appointed to the IRB, within the scope of available expertise needed to conduct its functions. The membership shall be diverse, so selection shall include consideration of race, gender, cultural backgrounds, clinical experience, and sensitivity to such issues as community attitudes, to promote respect for the membership's advice and counsel in safeguarding the rights and welfare of human subjects and to assess the research submitted for review. The membership of the IRB should represent the local community. Membership from across the system will be required.

Individuals who are responsible for business development are prohibited from serving as members or ex-officio members of the IRB and from carrying out day-to-day operations of the review process.

3. Composition of the Board

a. *Scientific Members*

The UCHealth IRB Committee will contain at least:

- Four physicians whose backgrounds represent areas in which research is taking place;
- One registered nurse (RN) from UCHealth; and
- One non-physician scientist such as a PharmD.

When an IRB encounters studies involving science beyond the expertise of the members, the IRB will use a consultant to assist in the review. However, when FDA-regulated products are reviewed, the convened meeting must include a licensed physician member.

b. *Non-scientific Members*

To increase diversity and decrease potential bias, members from the non-scientific community are included. Non-scientific members are individuals whose education, work, or interests are not primarily in medical or scientific areas. The UCHealth IRB Committee

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will contain a minimum of one member whose primary concerns are in non-scientific areas (for example: lawyer, ethicist, clergy member,) is required to establish a quorum at each meeting. At least one non-scientific representative must be present for all IRB meetings; if at least one is not present, the meeting will be canceled. (UCHealth IRB routinely has 2-3 non-affiliated, non-scientific members.)

c. ***Non-affiliated Members***

The UCHealth IRB Committee will contain a minimum of one representative who is not otherwise affiliated with UCHealth and who is not part of the immediate family of a person who is affiliated with UCHealth. The non-affiliated member(s), can be either a scientific or non-scientific reviewer. They should be knowledgeable about the local community and be willing to discuss issues and research from that perspective. Consideration should be given to recruiting individuals who speak for the communities from which the UCHealth will draw its research subjects. The non-affiliated member(s) should not be vulnerable to intimidation by the professionals on IRB, and the IRB should fully use the services of the non-affiliated members.

d. ***Alternate Members***

Each member is encouraged to find an alternate for him/herself in case of absences. Alternate members must be approved by the IRB Chairperson and must participate in the same orientation process as IRB members. Alternate Members must sign and agree to comply with the IRB confidentiality agreement. The IRB meeting minutes must reflect the attendance and participation of an Alternate Member. The Alternate Members' curriculum vitaes (CVs) must be kept on file with the IRB office. The purpose of alternate membership is to prevent canceling or postponing IRB meetings for a lack of quorum.

e. ***Representatives of Special/Vulnerable Groups of Subjects***

When certain types of research are reviewed, members or consultants who are knowledgeable about concerns of certain groups or local context may be required. For example, if an IRB reviews research involving prisoners, a member who can represent this group, either an ex-prisoner or an individual with specialized knowledge about this group must be included on the IRB. For more information on this subject see Section G regarding Vulnerable Subjects.

f. ***Chairpersons***

The individual IRB Chairperson will be a highly respected individual from within the UCHealth medical staff who is proficient in human subjects research. The Chairperson must be of sound and ethical character and reputation, without conflicts of interest that would curtail his or her ability to serve objectively and according to the mission of the IRB as defined in applicable laws, regulations, and policies. The Chairperson must be fully

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capable of managing the IRB and the matters brought before it with fairness and impartiality.

The IO appoints the IRB Chairperson, Vice Chairperson, and IRB members, after consulting with the Director of IRB Administration. The IO will appoint one of the existing physician members of the IRB to the role of Chairperson and Vice-Chairperson. The Vice-Chairperson will serve as Chairperson when the Chairperson is absent. In the rare case that both the Chairperson and Vice-Chairperson are called away from the meeting, the Chairperson may appoint an alternate Chairperson. This alternate Chairperson should be the most senior IRB member present, and this appointment will be for one meeting only.

The Chairperson and Vice-Chairperson bear the task of ensuring that the IRB is, and is perceived to be, fair and impartial and immune from pressure by the institution's administration, the Investigators, or other professional and non-professional sources in the IRB's evaluation of any given study.

REFERENCES

21 C.F.R. § 56.107

45 C.F.R. § 46.108(a)(2)

45 C.F.R. § 46.107

45 C.F.R. § 46.110(b)(1)

21 C.F.R. § 56.110(b)(2)

21 C.F.R. § 56.115(a)(5)

OHRP: IRB Guidebook; FDA Information Sheets: FAQ, Section II, Questions 14, 15, 17

B. NON-MEMBERS

1. IRB Staff (non-voting)

It is customary for the UCHealth IRB to include IRB staff at the board meetings. IRB staff report to the Institutional Official with day-to-day management by the director of IRB administration. The purpose of having IRB staff attend board meetings is to inform and communicate local concerns to the IRB. They act as advisors regarding federal regulations and may attend regular meetings as an alternate for members with comparable qualifications for the purpose of satisfying quorum requirements. The IRB Regulatory Coordinator will provide the first assessment of all submitted documents. The IRB Regulatory Coordinator will assist in presenting and organizing submissions for IRB Members' deliberation and determination.

2. Consultants

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The Chairperson may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the Board. These individuals may not be present for any deliberation by IRB members or vote with the regular and alternate members of the IRB, and their presence or absence will not be used in establishing a quorum for a Board meeting. Consultants with access to confidential information will be asked to sign a confidentiality agreement. (UCHealth has used MD specialists in the fields of surgery and pediatrics for example.)

3. Visitors at IRB Meetings

While IRB meetings are closed to the public, an IRB may permit visitors, subject matter experts, research staff, consultants, and students (collectively, "Visitors") to attend meetings provided that such Visitors have no actual or perceived conflict of interest. Research staff may attend the IRB meeting only while their studies are being discussed. All Visitors, other than legal advisors or students, must leave the meeting during deliberations and voting. Visitors will not participate in deliberation or voting. Nonmembers and Visitors will not count towards the quorum. Visitors must follow applicable guidelines.

All Visitors must obtain the IRB's permission to attend the meeting in advance. Visitors must sign in and agree to comply with the IRB confidentiality agreement. Visitors may observe the proceedings. However, with the exception of students, legal consultants, and officials from a government or regulatory body, Visitors may not take notes, secure any meeting materials, or record or otherwise preserve the IRB meeting content. Students may observe and take notes for academic purposes, but may not remove any proprietary information, including information related to protocols. Consultants and subject matter experts may attend to give information to the IRB as needed. Visitors, other than legal advisors and students, must leave the room during protocol discussions, deliberations, and voting.

The IRB meeting minutes must include the names of all attendees at the meeting, including all Visitors. The minutes must reflect that Visitors left the room and did not participate during protocol discussions, deliberations, and voting as provided under this policy.

REFERENCES

Minutes of Institutional Review Board Meetings: Guidance for Institutions and IRBs, U.S. Department of Health and Human Services: Office for Human Research Protection, Food and Drug Administration, Office of Good Clinical Practice, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Office of Regulatory Affairs, (September 2017), https://www.fda.gov/downloads/RegulatoryInformation/ Guidances/UCM470154.pdf

C. MEMBER & STAFF RESPONSIBILITIES

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1. General Member Responsibilities

Each IRB Member's primary duty is the protection of the rights and welfare of the individual human beings who are serving as participants in research. The reviewer must understand that he or she is not serving on the IRB to expedite the approval of research, but to serve as the link between the investigator and the participants. In order to fulfill his or her duties, IRB members are expected to be knowledgeable of the regulations governing human subject protection, biomedical and behavioral research ethics, and the policies of UCHealth relevant to human subjects research. The IRB must be, and must be perceived to be, fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources.

All members are expected to review all actions scheduled for convened review, be familiar with them, and be prepared to discuss the materials at the convened meeting. Different categories of members have specific expectations:

- Non-affiliated members are expected to provide input about their knowledge of the local community and be willing to discuss issues and research from that perspective.
- Non-scientific members are expected to provide input relevant to their knowledge, expertise, and experience, professional or otherwise. For example, members who are lawyers should present the legal views of specific areas that may be discussed. Non-scientific members should advise the IRB if additional expertise is required to assess if the protocols adequately protect the rights and welfare of research participants.
- Scientific members are expected to contribute to the evaluation of a study on its scientific and statistical merits and standards of practice. These members should also be able to advise the IRB if additional expertise is required.

2. Specific Member and Staff Responsibilities

Additional duties and terms for IRB members and staff are outlined in detail in the following tables.

Table 1: Member Responsibilities – Chairperson/Vice-Chairperson

Title	Chairperson/Vice Chairperson
Term	The term for IRB Chairperson is one year. This term is renewable without term limits. If unable or unwilling to fulfill his/her duties as IRB Chairperson, he/she may be removed from the IRB at any time by the Institutional Official.

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Responsibilities	In addition to the duties of IRB members, the Chairperson of the IRB assumes the following duties: • Conduct and preside over IRB meetings. • Call and conduct emergency IRB meetings, as necessary. • Review/approve appropriate requests for expedited and exempt reviews, according to IRB policy and consistent with federal regulations. • Review and approve or disapprove appropriate requests for Expanded Access Program (Compassionate Use), and Emergency Use IND applications, as permitted by IRB policies and federal regulations. • Recommend actions in emergency situations to protect research subjects and to remain in compliance with regulations. • Recommend new members for appointment to the IRB, • Review IRB Policies and Procedures at least annually and recommend changes, as necessary. • Advise investigators on policies, procedures, and regulations. • Possess an understanding of the UCHealth policies and procedures governing research, and applicable laws and regulations, including regulations issued by the FDA and OHRP. • Recommend for appointment a candidate for Vice Chair of the IRB. • Interact/communicate with Medical Staff, Medical Executive Committee, Chief Medical Officer, and others as necessary. • Ensure that the IRB performs the duties required by the IRB Policies and Procedures and federal and state statutes and regulations, including maintaining the necessary records. • The Chair or designee shall have the authority to act upon (approve, or move to modify) expedited reviews, minor amendments in the research protocol. Such action will be presented at the next regularly scheduled IRB meeting for discussion, comment and/or modification, as appropriate. Performs or delegates expedited review of research applications and revisions • Reviews reports of serious or unexpected adverse events or unanticipated problems. • Consults with Investigators as needed. • Obtains continuing education related to IRB responsibilities. **Chairpersons are empowered to suspend the conduct of a clinical trial determined to place individuals at unacceptable risk pending IRB review.** The Chairperson may appoint a Vice Chairperson to assist or act on behalf of the Chairperson in particular IRB matters and at IRB meetings on a case-by-case basis. The Chairperson also may delegate any of his/her responsibilities as appropriate to other qualified individual(s), in the event that the Vice Chairperson is also not

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	available. Email access is required as much of the IRB correspondence is electronically documented.
Time Commitment	The amount of time committed to adequately perform the responsibilities of Chairperson is often several hours each month but usually less than six. Participation in an additional preparatory meeting with the UCHealth IRB Director and Coordinator each month is routine. The Chairperson will participate in several hours of continuing education yearly.
Other Requirements	• CITI training requirements (IRB Member and Information, Privacy and Security Modules) must be kept current. • IRB Chairperson is responsible for providing input on the ongoing performance of the IRB office staff to the Chief Medical Officer/IO, as applicable.
Attendance	Attendance is required to maintain quorum. If the Chairperson misses three consecutive meetings or 50% of meetings annually, he/she will be requested to step down from the Board. Alternate members should be found in replacement to prevent this from happening.
Conflict of Interest (COI)	• Compliance with the CU Anschutz FCOI yearly training and disclosure requirements. • The potential for a conflict of interest must be disclosed prior to conducting a review of research. Conflicts of interest could include close personal or professional relationship to an Investigator, or interest, financial or otherwise, in the outcome of the research.
Compensation	Compensation is contracted with the Chief Medical Officer according to UCHealth guidelines for Department Medical Directors.
Liability Coverage	UCHealth maintains Insurance Warranty for all claims made against IRB members, alternates and consultants.
Removal	The IRB Chairperson can be removed only by the membership of the IRB for failure to meet performance requirements of the position. If there are concerns regarding loss of privileges, license or non-compliance, the signatory official or senior management will inform the IRB membership, and the IRB will take appropriate action. The position is dependent on active, good standing with medical staff and UCHealth administration.

Table 2: Member Responsibilities – IRB Member/Alternate Member

Title	IRB Member
Term	The term for IRB members is one year. This term is renewable without term limits. Members who are unable or unwilling to fulfill their duties as IRB members

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	may be removed from the IRB at any time by the IRB Chairperson and/or Institutional Official.
Responsibilities	• Attend monthly convened IRB meetings and occasional emergency meetings • Review submitted research within appropriate timelines. Full Board Reviews should be completed within 1 week prior to attending the meeting. Expedited reviews should be completed within 3 business days prior to attending the meeting. • Responsible for the review of all agenda items even if not assigned as primary reviewer (adverse events, deviations, data safety monitoring reports, minutes, etc.) • Act as primary reviewer for assignments and provide summaries at the meeting. • Complete electronic review checklists in IRBManager for all assignments according to the timelines listed above. • Consult with Investigators and IRB staff as needed • Participate in continuing education related to human subject protection
Time Commitments	Generally, several hours per month are required. IRB members are required to alert the IRB Regulatory Coordinator in advance if they cannot attend an IRB meeting. Their alternate will assume their responsibilities if possible. See Section IV.A.3.d discussing alternate members. If they cannot notify the IRB Regulatory Coordinator in a timely manner, they are expected to deliver written comments to the IRB Regulatory Coordinator to be used for discussion only, but not for absent voting purposes.
Attendance	Attendance is required to maintain quorum. If a member misses three consecutive meetings or 50% of meetings annually, he/she may be requested to step down from the Board. Alternate members should be found in replacement to prevent this from happening.
Conflict of Interest (COI)	Compliance with the CU Anschutz FCOI yearly training and disclosure requirements. The potential for a conflict of interest must be disclosed prior to conducting a review of research. Conflicts of interest could include close personal or professional relationship to an Investigator, or an interest, financial or otherwise, in the outcome of the research.
Other Requirements	CITI training requirements (IRB Member and Information, Privacy and Security Modules) must be kept up to date.
Compensation	Non-employed members may be eligible for a stipend for their time, travel, and mileage.
Liability Coverage	UCHealth maintains Insurance Warranty for all claims made against IRB members, alternates and consultants.

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Removal	If there are concerns regarding loss of privileges, license or non-compliance, the signatory official or senior management will inform the IRB membership. The position is dependent on active, good standing with Medical and Nursing staff privileges.

Table 3: Director of IRB Administration Responsibilities

Title	Director of IRB Administration
Hours	Exempt
Location	IRB Department # 0100-7025
Responsibilities	Job Description and Performance Evaluations • Responsible for the day-to-day management of the system UCHealth IRB department and IRB Members for the protection of human research subjects. The Director of IRB Administration reports to the Institutional Official. The Director of IRB Administration acts as an advisor regarding federal regulations and may be appointed as an alternate for scientific members with comparable qualifications for the purpose of satisfying quorum requirements. • Responsible for not human subject research and exempt determinations • Reviews and triages reports of internal adverse events, deviations, unanticipated problems and reports of potential non-compliance • Performs or delegates the review of all submitted Investigator reports and determines if there is a reason for full IRB review. • Is the direct liaison from the IRB to the Institutional Official and health system for research protections and compliance issues, problem solving and system communication. • Responsible for establishing personnel requirements and for hiring and evaluating the ongoing performance of IRB support staff and members. **Staff Positions** • Staffing levels and function allocation will be determined according to UCHealth policy based on management assessment of support requirements and budget constraints. **Evaluation of Job Performance**

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	• The job description and performance evaluation process of the Director of IRB Administration is performed by the Chief Medical Officer and the Institutional Official as established and conducted according to UCHealth Policies. • The Director of IRB Administration will direct the performance evaluation process for the IRB staff.
Conflict of Interest (COI)	Compliance with the CU Anschutz FCOI yearly training and disclosure requirements. The potential for a conflict of interest must be disclosed prior to conducting a review of research. Conflicts of interest could include close personal or professional relationship to an Investigator, or interest, financial or otherwise, in the outcome of the research.
Other Requirements	RN License IRB Certification CITI Training Requirements (IRB Member and Information, Privacy and Security Modules)

Table 4: IRB Regulatory Coordinator

Title	IRB Regulatory Coordinator
Hours	Exempt
Location	IRB Department # 0100-7025
Introduction	UCHealth has established the position of IRB Regulatory Coordinator to manage the day-to-day operations of the IRB.
Responsibilities	Performs or delegates the intake of all submitted Investigator reports. The IRB Regulatory Coordinator will perform the first assessment of submitted materials. The IRB Regulatory Coordinator will assist in presenting and organizing submissions for IRB Members' deliberation and determination. See Section VI.A discussing pre-review. **Delegation Of Authority Or Responsibility** Signature authority for IRB determinations has been delegated to the IRB Regulatory Coordinator. Other duties and authorities may be delegated on a case-by-case basis by the IRB Chairperson and/or Institutional Official. The IRB Regulatory Coordinator is ultimately responsible for reporting to the Institutional Official. **Alternate Member of IRB**

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	The IRB Regulatory Coordinator will act as an advisor regarding federal regulations and may attend regular meetings as an alternate for any non-scientific member for the purpose of satisfying quorum requirements. **Directs the administrative functions of the IRB by:** • Coordinating submissions with the investigators and their staff • Assuring research compliance with guidelines set by the FDA and UCHealth IRB • Providing guidance to researchers and their staff on maintaining accurate documentation of IRB actions: **Ensuring Investigators and Sponsors are informed of the actions and findings of the IRB:** **Regulatory Tracking** • Maintaining CITI training requirements tracking for investigators, IRB members and research staff • COI Yearly Disclosures • Medical Credentialing
Conflict of Interest (COI)	Compliance with the CU Anschutz FCOI yearly training and disclosure requirements. The potential for a conflict of interest must be disclosed prior to conducting a review of research. Conflicts of interest could include close personal or professional relationship to an Investigator, or interest, financial or otherwise, in the outcome of the research.
Other Requirements	CITI Training Requirements (IRB Member and Information, Privacy and Security Modules) Certified IRB Professional (CIP)

Table 5: IRB Data Specialist/Administrative Assistant Responsibilities

Title	IRB Data Specialist/Administrative Assistant
Hours	Non-exempt
Location	IRB Department # 0100-7025
Introduction	The IRB has established the position of IRB Data Specialist/ Administrative Assistant to assist the IRB department.
Responsibilities	Instrumental in supporting the administrative functions of the IRB department:

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	• Maintains audit-ready files, both paper and electronic • Provides pre-screening for all IRB submissions • Maintains regulatory data base • Analyses and extracts reports from regulatory data base • Prepares and distributes monthly meeting packets to IRB members • Maintains accurate documentation of IRB determinations and meeting minutes • Assists with scheduling meeting room and catering for the monthly IRB meeting as well as other related IRB meetings. Provides Administrative Assistant support to the Director of IRB Administration and the Director of Research Administration.
Other Requirements	CITI Training requirements (IRB Member and Information, Privacy and Security Modules) Conflict of Interest training and disclosure yearly per CU Anschutz requirements

REFERENCES

45 C.F.R. § 46.107

21 C.F.R. § 56.107

45 C.F.R. § 46.110(b)(2)

21 C.F.R. § 56.110(b)(2)

OHRP: IRB Guidebook; FDA Information Sheets: FAQ, Section II, Question 17

D. MANAGEMENT OF THE IRB MEMBERSHIP

The management of the membership of the IRB and administrative oversight of member appointments, IRB-related activities, communications, and other administrative details related to IRB membership are the responsibility of the UCHealth Director of IRB Administration.

1. Member Terms

Members, including the Chairperson, will serve on the IRB for at least a period of one year subject to such Member's or Chairperson's compliance with their respective responsibilities. Terms last one year. Reappointment for additional terms may occur by mutual agreement of the IRB Chairperson and members.

2. Appointment

a. *Appointment of Members*

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The IO appoints the IRB Chairperson, Vice Chairperson, and members, in consultation with the Director of IRB Administration. Members will be nominated from a variety of sources, including previous and current IRB members, department chairs, compliance administrators, and various public groups.

When an individual is nominated or when an individual expresses interest in serving on the IRB, a copy of the individual's CV will be requested and the nominee will be invited to observe and IRB meeting. The nominee's CV and any relevant correspondence are reviewed by the Director of IRB Administration and recommendations are made to the UCHealth IO. Nominees appointed to serve on the IRB receive a letter of appointment signed by the IO.

b. *Appointment of Consultants*

During the review process, the IRB may determine that a consultant's input is required. IRB staff or the IRB Chairperson may determine that a consultant is required during pre-review, or members of the IRB may request a consultant's review at any time during the review process. This determination or request will be based on the topic of the protocol and the expertise of the voting members. The Chairperson, Chief Clinical Research Officer, or Director of IRB Administration will select a consultant. The Chairperson may consult with the Principal Investigator (PI), department chair, or any other individual deemed appropriate to determine a suitable consultant. A consultant may be either internal or external to UCHealth.

Consultants will be asked to disclose any potential conflicts of interest before working with the IRB. If a conflict exists, a different consultant will be selected.

Consultants may be asked to review a protocol or provide education on a topic of specific concern to the IRB and provide the information by written report or attend a meeting, or both. Key information provided by the consultant will be documented in the minutes, and any written reports or other documentation of consultant reviews will be maintained in the protocol file.

The consultant may participate in all discussions, but may not participate in deliberations and may not vote. Use of consultants will be documented in the meeting minutes, as this will be presented to the convened IRB during the discussion of the protocol. For expedited review submissions, consultant reports will be documented in the protocol file.

3. Evaluation of IRB Members

IRB Members, including the Chairperson and Vice Chairperson, will be asked to complete self-evaluation forms on an annual basis and submit the forms to the appropriate members of the IRB staff. The IO, in conjunction with appropriate staff members, will review the self-assessments periodically to determine education and training needs and to make decisions regarding continuation of IRB Membership.

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The IO will regularly assess and adjust membership and composition of the IRB to meet regulatory and organizational requirements.

Investigators, employees, and sponsors are prohibited from exerting undue influence over the IRB, any of its members or staff, investigators, or any other member of the research team in order to obtain a particular result, decision, or action. “Undue influence” means attempting to interfere with the normal functioning and decision making of the IRB or to influence an IRB member or staff, and investigator or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision or action by the IRB, or any of its members or staff.

IRB members and staff will report undue influence to the IO. The IO is responsible for the initial investigation. Additional institutional officials, such as the Chief Medical Officer, Chief Executive Officer, or other compliance officials, may be notified, as appropriate, of allegations of undue influence and may be asked to review and endorse a corrective action plan.

4. Resignations and Removals

A member of the IRB, including the Chairperson, may resign before the conclusion of his or her term. The vacancy will be filled as quickly as possible. If an IRB member is not adhering to his or her responsibilities, a written summary of concerns must be submitted to the IRB office. A member may be removed by the IRB Chairperson or the IO at any time.

5. Compensation

Participating as an IRB member is voluntary. Compensation for the IRB Chairperson is determined per UCHealth guidelines. Although most members are not compensated, community members are given the option to receive a stipend for time, travel, and mileage.

6. Liability Insurance

Regular and alternate members have liability insurance coverage as part of their IRB membership in their capacity as agents of UCHealth for the actions taken in such capacity.

E. Training and Resources for IRB Members

1. IRB Training Policy

Members of the IRB who are overseeing research on human subjects at UCHealth will receive initial and ongoing training regarding the responsible review and oversight of research. As part of its commitment to human subject protection, UCHealth has mandated training requirements for staff of research offices, IRB members, IRB staff, and for individuals engaged in the conduct of human subjects research. Documentation of initial and ongoing training is recorded by the IRB department.

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Collaborative Institutional Training Initiative Program (CITI) web-based training is recognized internationally as the foundational research educational requirement. The health system offers it as a free educational offering for its employees involved in research projects or in service to the IRB committee. Renewal of CITI is required every 3 years.

a. *IRB Members*

All new IRB members, including alternate members and consultant members will meet with the Director of IRB Administration for an informal orientation. At the orientation session, the new member will be given an IRB Member Handbook (binder) that includes:

- The Belmont Report
- UCHealth Policies for the Protection of Human Subjects
- Federal regulations relevant to the IRB
- Instructions for the electronic IRB review process

New members must complete the following requirements before they may serve as a reviewer:

- Complete the IRB Orientation Training
- Observe one IRB meeting (assignments will be given only as a training exercise and they will not be able to vote at their observation meeting)
- Complete the CITI Human Subject Research – IRB Member and Information Privacy and Security Modules. Renewal of these modules is required every 3 years.
- Complete Financial Conflict of Interest Training and Disclosure. This requirement must be completed annually.
- Submit a signed curriculum vitae every two years
- Sign a confidentiality agreement

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

- Training workshops
- Distribution of copies of appropriate publications
- Webinars

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- Identification and dissemination by the Director of IRB Administration of new information that might have affected the human research protection program via email, mail, or during board meetings

IRB members and staff must be familiar with the UCHealth IRB Standard Operating Policies and Procedures (SOP). They will be encouraged to participate in other educational opportunities focused on IRB functions. UCHealth will support such activities to the extent possible and as appropriate to the responsibilities of members and staff.

b. *IRB Office Staff*

IRB Office Staff must complete the following requirements:

- Complete the CITI Human Subject Research – IRB Member and Information Privacy and Security Modules. Renewal of these modules is required every 3 years.
- Complete Financial Conflict of Interest Training and Disclosure. This requirement must be completed annually.
- Submit a signed vitae every two years
- Sign a confidentiality agreement

IRB Office Staff will be encouraged to become Certified IRB Professionals.

c. *Principal Investigators and Research Staff*

Principal Investigators, co-investigators, and research staff listed on human research protocols must complete the following requirements:

- Successfully complete the CITI Human Subjects Research Module and CITI Information Privacy and Security Module *prior to submitting a protocol*. These modules are completed every 3 years.
- Complete annual Financial Conflict of Interest Training and Disclosure
- Submit a signed curriculum vitae every two years
- Sign a confidentiality agreement

Until the above items are completed, an investigator and/or research staff may not be assigned or request participation on a research project.

2. Resources

UCHealth supports the function of the IRB and provides office space and equipment for the IRB staff to adequately manage federally required data provisioning demands of the IRB and Research Protection Program. To accommodate security of proprietary information, confidentiality and protection of patient health information, the office/work

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areas must offer limited access to non-IRB staff and be within close proximity to the IRB department. Additionally, meeting areas should be adequately equipped and afford confidential and private conference discussion/presentation, video presentation, and teleconferencing. The room should be large enough to allow for catering set-up and accommodate IRB members, IRB staff, and investigative presenters.

3. Reference Materials

Federal updates, newsletters and publications are provided to IRB members at meetings, via web or in the IRB office. Members and IRB staff are encouraged to attend sponsored webinars and educational offerings.

V. FUNCTIONS AND OPERATIONS

A. IRB MEETING ADMINISTRATION

Except when an expedited review procedure is used, the IRB will review proposed research at convened meetings at which a quorum is present.

1. Meeting Schedule

The IRB will meet monthly, or at some other frequency, as determined by IRB Chairperson and the IRB department. The IRB routinely meets on the second Wednesday of every month. Just-in-time meetings are convened if necessary to address patient need or safety concerns. Meetings are convened at a meeting room with video conferencing capabilities. The schedule of meetings is distributed during the last quarter of the year for the upcoming year. In addition, calendar invites are sent to members that have provided email addresses.

2. Meeting Materials

a. *Distribution of Materials*

All IRB members will receive complete study documentation no later than one week in advance of the meeting to allow time for adequate review. Materials will be made available in IRBManager. Email notification is sent when all materials are ready for review. A hard copy of materials may be provided upon request.

Materials include:

- Agenda
- Reviewer Materials for All IRB Members
    - Research Protocol

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- IRB Application
- Proposed Informed Consent document(s)
- HIPAA authorization (if not part of the informed consent form) or request for waiver
- Any materials that participants/subjects will interact with, including surveys, questionnaires, education materials, calendars, or videos, etc.
- Advertising intended to be seen or heard by potential subjects, including email solicitations, physician letters, or any other recruitment materials
- Investigator's Brochure (if applicable)
- Department Director Approval as applicable

b. *Confidentiality*

All material received by the IRB will be considered confidential and will be distributed only to meeting participants (regular members, alternate members and special consultants) for the purpose of review. All application materials will be stored in an IRB study file with access limited to IRB members and staff. Consultants and visitors will be expected to sign confidentiality agreement if they are not credentialed employees, students, or UCHealth consultants.

c. *Destruction of Copies*

All material received by the IRB that is considered confidential and in excess of the required original documentation and other appropriate uncontrolled forms will be collected at the end of the meeting and destroyed by a method deemed appropriate by the Director in compliance with applicable UCHealth policy(ies) related to destruction of confidential information.

3. Primary Reviewers

Prior to the meeting, the IRB department will designate primary reviewers for each research proposal. The primary reviewers' responsibilities include:

- Reviewing all protocol materials for their required assignment
- Determining the presence of the required elements for consent
- Assessing risk determination
- Establishing scientific merit and overall adherence to sound research protection guidelines

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The primary reviewers will receive and review the current protocol including any amendments to protocol since initial review. They are responsible for presenting a brief description of the protocol and their findings at the meeting. Any IRB member may access the complete IRB protocol file and relevant IRB minutes prior to the convened meeting that are related to their assignment. Optimally a physician, nurse, and non-scientific member are responsible for the primary review of each agenda item.

4. Conflicts of Interest

No IRB member will participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. If an IRB member has a conflict of interest or conflict of commitment for a study on the agenda, the member may remain in the room for the presentation of the study and initial questions, but must leave the room during the discussion and vote on the protocol. If the member is participating via teleconference, he or she will put the call on hold until they receive a text message notifying him or her to return to the meeting. The IRB member will not be counted as part of quorum. The meeting minutes will document that the IRB member with the conflict left the room or call during the discussion and voting.

5. Roles of Subcommittees

The use of subcommittees will be based on need. A subcommittee may be formed for additional discussion regarding compliance, risk, policies, or controverted issues. The results of the subcommittee review are presented at the convened IRB.

6. Retrospective Review of Emergency Use of Investigational Articles or Devices

An investigational article may be used in an emergency prior to IRB review. This situation occurs when the patient is in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. Such emergency use is reported to the IRB within five working days, and any subsequent use of the test article is subject to prior IRB review (see Section VII. C. for more information).

7. Documentation of Approval

A majority of members must vote in favor of an action for that agenda item to be accepted by the IRB. Only regular and alternate members acting in place of absent regular members may vote. The vote will be recorded in the minutes. Members with a conflict of interest will recuse themselves from the discussion and voting and such will be noted in the minutes. See Section VI.C.6.a (discussing IRB determinations).

REFERENCES

45 C.F.R. § 45.108(a)(3)

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21 C.F.R. § 56.108(a)

Emergency Use of Unapproved Research Device or Drug Policy

B. VOTING

1. Quorum

A quorum is required for the IRB to transact in any business. If a quorum is not present, the meeting will be canceled. A quorum is fulfilled when one half (50%) plus one member is present for voting purposes. A quorum consists of regular and/or alternate members. Special consultants may not be used to establish a quorum.

Quorum must include at least one member whose primary concerns are in scientific areas, one member whose primary concerns are in non-scientific areas, and one member from each local community (e.g., UCHealth North and UCHealth South). If the IRB is reviewing research that involves categories of vulnerable participants, one or more individuals who are knowledgeable about or experienced in working with such participants must be present. See Section IV.A). If members leave the room and quorum is lost, then votes cannot be taken until a quorum is restored, even if half the members are still present.

When FDA-regulated research is reviewed, one member who is a physician must be present. Because a large majority of trials at UCHealth are FDA regulated, at least one physician-member always must be present.

A member may be used to establish a quorum, even if he or she abstains from voting. If a member has not reviewed an agenda item or items, he or she will be expected to abstain from the discussion and vote for those items, but the member will still count towards the quorum.

A member experiencing a conflict of interest or commitment situation must recuse him/herself. If a member recuses him/herself from deliberations and voting, the member may not be used to establish quorum for the duration of review of the item from which the member is recused. Recused members must leave the room during voting and deliberation of the item from which the member is recused.

2. No Proxy Voting

Proxy voting is not acceptable by written notification, email, texting, or telephone (single phone call). Teleconference voting is allowed if the members are participating in the discussion of the protocol and have received all review materials.

On occasion, meetings may be convened with the assistance of a telephone conference call. A quorum (as defined above) must participate physically or utilize the conference call meeting as a means of involvement. To allow for appropriate discussion, all members must be connected simultaneously for the conference call and must have all documentation to review. “Telephone polling” (where members are contacted individually)

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will not be accepted as a conference call. The minutes of the meeting will document which members, if any, participated in the convened meeting via telephone conference or video conference.

Members must either be present at the convened meeting or participating in the conference call in order to vote on an issue discussed during a convened meeting.

3. Voting

Members of the IRB vote upon the recommendations made by the primary reviewers according to the criteria for approval. If quorum is lost during a meeting, the IRB cannot take votes until it is restored.

Votes are taken in the convened meeting and documented in the minutes by the IRB staff member serving in the administrative function. The IRB will make its determination, described in Section V.B.4 and VI.C.56 below, and determine the level of risk and frequency of review for each protocol.

If an IRB staff member is serving on the IRB as a regular or alternate member, then that staff member may not be responsible for any administrative functions during that meeting. Specifically, he or she will be expected to contribute to the discussion as a substantive participant.

4. IRB Actions & Determinations

The IRB may make one of the following determinations as a result of its review of research submitted for initial review or for continuing review:

- Approve the research;
- Approve the research with a condition or contingency;
- Defer or table the research; or
- Disapprove the research.

Except when the expedited review procedure is used, these actions will be taken by a vote of a majority of the regular and alternate members present, except for those members present but unable to vote in accordance with IRB's conflict of interest policies. When reviewing a protocol via expedited review, the Chairperson or designee will make any of the following determinations except disapproving a study. All determinations and any required actions will be reported in writing to the Principal Investigator and recorded in the minutes.

REFERENCES

Research Conflict of Commitment and Conflict of Interest Policy

C. APPEAL PROCESS

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1. Purpose

The purpose of an appeal is to give the PI an opportunity to request reconsideration of a decision reached by the IRB and/or its subcommittees. The researcher may feel:

- He or she has more information to share with the IRB,
- The sanction or judgment is too hard or restrictive, or
- Policies or procedures have not been followed.

2. Timeframe

The Principal Investigator has 30 days to submit their appeal and the IRB has 30 days to respond to the appeal.

3. Process

- For issues not including suspension, termination or non-compliance (for example a tabled first application) the researcher may appeal/negotiate their position by submitting information via email to the IRB staff to forward to the IRB Chairperson. Examples include:
    - Submitting collaborative or supportive documentation regarding risk/benefit.
    - Providing names of consultants supportive of the research.
    - Modifying the application according to the IRB requirements.
- For appeal of IRB decision that involve suspension, termination, non-compliance, the researcher should submit a written appeal in the form of a letter to the IRB staff that details:
    - The issue that prompted the Board's decision.
    - A corrective action plan that has been implemented.
    - Documented evidence that the issue has not reoccurred or is resolved.
    - Any additional documentation that provides evidence that the safety and/or confidentiality of study subjects will be protected and that the scientific integrity of the study, the Code of Federal Regulations, and IRB SOPs will be adhered to.
- An ad-hoc subcommittee of the UCHealth IRB will be brought together by the chairperson to decide if the appeal will be considered. Consultants may be used as needed. Approval, disapproval or contingencies will be decided upon and reported back to the convened IRB.

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- The convened IRB will determine to uphold the original decision (disapprove), modify, approve and/or reinstate the PI.
- The Principal Investigator may be required to provide additional provisions to the protocol, obtain education, or modify the corrective action plan.
- If the IRB choses to suspend, terminate, or withdraw approval following appeal (allow initial disapproval decision to stand), the decision is final. No other entity within the health system may override the decision.

4. Example Corrective Action Plans

Corrective action plans (CAPs) must address the following:

- The factors that contributed to the issue;
- New processes, forms, research designs, etc. that have been implemented to correct the issue; and
- The Principal Investigator's role in the CAP must be outlined with a description of how the incident will be prevented in the future.

5. Notifications

Lastly, if a protocol is suspended, terminated or withdrawn (on a permanent basis) and appeal is not successful, all institutional personnel and federal agencies (OHRP, FDA, and ORI) must be notified.

D. RECORDS & DOCUMENT MANAGEMENT

The IRB's files must contain a complete history of all IRB actions related to review and approval of a protocol, including scientific reviews, continuing reviews, modifications, reports of an unanticipated problem increasing risks to participants and others, subject complaints (which will be kept in an independent file), reports of serious or continuing noncompliance, and adverse event reports. All records regarding a submitted study (regardless of whether it is approved) must be retained in an appropriate manner as required by regulations and institutional policy(ies).

Filed records are accessible for inspection and copying by authorized representatives of the sponsor, funding department or agency, regulatory agencies, and institutional auditors at reasonable times and in a reasonable manner.

1. Document Retention

The IRB shall retain all records regarding a project or protocol application (regardless of whether it is approved) for at least three years. For all applications that are approved and the research initiated, the IRB must retain all records of that research for at least three years after the completion of the research or termination of IRB approval. If a protocol is

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cancelled without participant enrollment, IRB records must still be maintained for at least three years after cancellation.

If the IRB record contains any PHI, the record must be maintained for six (6) years. During this period, these records shall be available to IRB members and to authorized representatives of the sponsor, the FDA, HHS and/or OHRP for the purposes of inspection and copying. Research studies that involve children shall be maintained until the child reaches the age of majority plus ten (10) years. Studies that involve incapacitated subjects will be maintained indefinitely.

In order to allow a reconstruction of a complete history of IRB actions related to the review and approval of the protocol, the IRB records include copies of all materials reviewed by the IRB.

2. Study-Related Documents

Documentation of IRB's activities must be prepared, maintained, and retained in a secure location adjacent to the IRB offices. Retained documents should include:

- Agendas and minutes for all IRB meetings, including documentation actions taken;
- Copies of all original research protocols reviewed, scientific evaluations, (if any, that accompany the proposals,) approved consent documents, progress reports submitted by Investigators, and reports of adverse events occurring to subjects and reported deviations from the protocol;
- Copies of all revised protocols and IRB approved protocols;
- Copies of all consent documents as originally presented, as well as copies of revised and approved consent documents;
- Copies of grant applications/research proposals that have been submitted to the IRB for review will be maintained with the protocol file;
- All correspondence with local hospitals, universities, and PI's will be maintained in the correspondence file with the corresponding contract or submission documents;
- Copies of all submitted monitoring reports, site visit reports and other continuing review activities;
- Copies of all correspondence between the IRB and the investigators;
- Statements of significant new findings provided to subjects;
- Reports of any complaints received from subjects;
- Reports of injuries and/or deaths of study subjects, unexpected or unanticipated reactions, continuing review documents, termination documents and reviews;
- Records of studies disapproved, suspended or terminated by withdrawal of IRB approval;

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- Progress reports submitted by investigators and records of continuing review activities;
- Records of all completed studies;
- For the initial and continuing review of research by expedited procedure, the file must include the specific permissible category, a description of the action taken by the reviewer, any findings under the regulation, and the frequency for the next continuing review;
- For exemption determinations, the file must include the specific category of exemption;
- Unless documented in the minutes, the file must include the determinations required by the regulations and protocol-specific findings for waiver or alteration of the consent process; research involving pregnant women, fetuses, and neonates; research involving prisoners; and research involving children;
- Emergency Use reports;
- Budget and accounting records as appropriate; and
- Back-up study documents are electronically accessible as well.

3. IRB Administration Documents

The IRB must maintain and retain all records related to IRB activities that affect review activities for at least three years, including the following:

a. *Member Rosters*

Rosters of regular and alternate IRB members identified by name, earned degrees, representative capacity, and indications of experience sufficient to describe each regular and alternate member's chief anticipated contribution to the IRB's deliberations; and any employment or other relationship between each member and IRB and/or UCHealth (e.g., full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant).

Alternate members shall be included on the roster. In addition to the above information, the roster shall indicate the regular member for whom the alternate may substitute.

Current and obsolete membership rosters will remain in the IRB Office. The roster of IRB members must be submitted to OHRP for registration purposes. Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of an FWA. In the latter case, changes in membership must be reported to OHRP.

b. *SOPs & Delegations of Authority*

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Current and obsolete versions of these SOPs will be maintained in the IRB office. Appropriate delegation of specific functions, authorities, or responsibilities by the IRB Chairperson also must be documented in writing and filed in the IRB Office.

c. *Meeting Minutes*

The federal regulations for the protection of human subjects require that the minutes of IRB meetings "show attendance at the meeting; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining or recusing; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution." These are minimum requirements.

The IRB staff person or designee will take minutes and use voice recording of each meeting to assist with transcription of minutes. Minutes will be written in sufficient detail to show the following:

- Meeting attendance and conflicts of interest, if any exist. All those attending will be included for example, consultants, Visitors, students, and presenters. The minutes will document that guests or IRB members with a conflict of interest are only present at appropriate times and leave during deliberations and voting when necessary.
- Actions taken by the IRB on each agenda item requiring full IRB action—including the basis for requiring changes in or disapproving the research.
- Summary of the discussion of controverted issues and resolution.
- Voting results, including the number for, against, and members who recused themselves and reason for recusal.
- Minutes will be distributed to members at the next IRB meeting for review and approval.
- Corrections requested by the IRB will be made by the IRB staff or designee, and the minutes will be printed in final form. The Chairperson of the IRB shall sign and date final, approved minutes.
- The IRB Regulatory Coordinator will maintain copies of the minutes, as well as the agenda and pertinent materials on file.
- Voice recording is destroyed each month upon transcription of minutes.
- Minutes are the confidential property of the IRB department. They are not routinely shared with any entity or individual outside the IRB and UCHealth reporting structures. Redacted portions of the minutes that pertain to a specific protocol or concern will be shared as necessary with investigators. Minutes will be shared with the FDA and other federal agencies as required during their on-site visits or upon request.

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d. *Communications To and From the Institutional Review Board*

All communications from investigators or any UCHealth entity or committee, shall be in writing and shall be retained as part of the records of the IRB. This requirement shall be waived at the reasonable discretion of the IRB Chairperson. Such communications may include but not be limited to:

- Questions about a study
- Revisions required on a protocol or informed consent document
- Approval or disapproval of a study and the reasons
- Adverse reactions, deaths, unanticipated effects or other data relating to a study
- Continuing review
- Suspension or termination of a study
- Any non-compliance on the part of an investigator

4. Destruction of Copies

All material received by the IRB, which is considered confidential and in excess of the required original documentation and appropriate controlled forms, will be collected at the end of the meeting and destroyed in compliance with applicable UCHealth policy(ies) related to destruction of confidential information.

5. Handling of Protected Health Information

There are occasions where the PI will submit documents to the IRB that contain Protected Health Information (PHI). In an effort to maintain the confidentiality of the patients, the IRB staff will remove, where possible, the PHI before it is submitted for further review. Disclosure of PHI is not routinely required for the IRB. The IRB will never disclose PHI to outside entities.

When documents are submitted to the IRB that include PHI, a copy of the document is made and all PHI is removed with either whiteout/permanent marker or using a text box to cover PHI and then the file is saved as a PDF. If the documents were submitted electronically, the PHI is deleted. In all departmental and IRB reporting, the names of patients are not used. The IRB will use a subject number which is de-identifiable. The original document containing the PHI is maintained in a separate red file folder within the protocol file.

The modified version of the document becomes the file copy for the IRB. This version will be submitted to the IRB Board Members for review. Once approved or acknowledged, this modified version will be stamped and maintained in the IRB protocol file.

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REFERENCES

45 C.F.R. § 46.115(a)(2)

E. RELIANCE ON EXTERNAL IRB

All research involving human participants and all other activities that involve such research, even in part, regardless of sponsorship, must be reviewed and approved by an IRB. Based on existing UCHealth agreements, research conducted at UCHealth Metro Denver facilities or by CU Anschutz faculty is not subject to UCHealth IRB authority or jurisdiction and is reviewed by the Colorado Multiple IRB (COMIRB) in accordance with an approved written agreement (see Section I. E.). Research subject to COMIRB jurisdiction does not constitute ceding by the UCHealth IRB, therefore, prior review and approval by the UCHealth IRB and submission of research related documents, including a ceding application, are not required. Under certain conditions, UCHealth may rely on another organization's IRB to review research subject to UCHealth IRB authority. The reliance on another IRB will be outlined in an approved IRB authorization agreement or under the conditions of an approved cooperative agreement.

For multi-site trials, each participating site that is engaged in human subjects research is responsible for obtaining IRB approval of their research activities from their local site's IRB or the execution of a reliance agreement with another IRB. A local IRB may rely upon review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. The reliance on another IRB must be outlined in an approved IRB authorization agreement or under the conditions of an approved cooperative agreement.

When the UCHealth IRB agrees to rely on the review of another qualified IRB, that other IRB, as the IRB of Record, will conduct the ethical review and determination that the criteria for IRB approval have been met and will be responsible for performing all IRB-related functions and reviews.

REFERENCE

Guidance: IRB Approval of Research and Guidelines for Conducting Research

F. COMMUNICATIONS

1. Internal

a. *Introduction*

It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of a research project directly to the appropriate institutional officials. It is vital that IRB members, department heads, and other officials with responsibility for oversight of research have open and ready access to the highest levels of authority within the system, institution and the research teams. All approval and disapproval notifications from the IRB are to be in writing. It is important that

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open and frequent communication with the investigative team be maintained with the IRB department and board.

b. *Investigator Notifications*

IRB Submissions: Principal Investigators will be notified in writing within two weeks of the meeting regarding action taken by the IRB for any continuing reviews or revisions. The stamped approval and expiration dates will appear in the footer/header of the approved Informed Consent Form.

Notification of protocol and informed consent document approval: Principal Investigators will be notified in writing of the approval. The IRB-approved consent form will be dated with the period of approval and submitted to the Principal Investigator with the approval letter. The stamped approval and expiration dates will appear in the footer/header of the approved Informed Consent Form. This stamp is electronically produced and therefore the footer should remain clear or the stamp will overwrite text that is in the footer. A Statement of Compliance is included in all initial and continuing review approval letters.

Acknowledgement of Submitted Documents: A formal acknowledgement letter is not generated upon submission of documents unless specifically requested by a sponsor.

Sponsor Communication: If a sponsor requires notification of approval, this condition is satisfied by the PI forwarding the IRB approval letter to them. Direct communication between the IRB and sponsor may occur to discuss issues or to answer questions.

Disapproval: Correspondence will provide the reason(s) for disapproval and instructions to the Principal Investigator for appeal of this decision. Refer to Section V.C Appeal Process and the Research Administration Policy Responding to Allegations of Research Misconduct.

2. External IRB Communications

The IRB is required by federal regulation and institutional policy to communicate certain actions to entities that may have an interest in the status of the research being conducted. All communications (letters, responses, etc.) that go to state or federal agencies related to human subjects research and the IRB must be approved by the IO prior to submission.

a. *IRB Reportable Events*

The purpose of this procedure is to ensure prompt reporting to appropriate institutional officials, funding sources, agency heads, regulatory agencies and departments such as OHRP and/or FDA and any other appropriate entity about:

- Unanticipated problems involving risks to human subjects or others
- Any serious or continuing non-compliance with the regulations or the requirements and determinations of the IRB.

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- Suspension or termination of IRB approval for cause such as non-compliance. The IRB will notify the Institutional Official and, as appropriate, federal agencies based on sponsorship/funding.

IRB reports to the Principal Investigator and Sponsor:

- Prospective emergency research: If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in 21 C.F.R. § 50.24 for an exemption from the informed consent requirements for emergency research, notification of disapproval will be conveyed to the Sponsor as well as the Principal Investigator.
- Device studies: If the IRB determines that a study submitted as a non-significant risk presents significant risk, the IRB must notify the Principal Investigator, and where appropriate, Sponsor.
-

b. *Information to be Included in IRB Incident Reports*

Communication to federal agencies will be in the format of an incident report. OHRP suggests that an incident report contain the following information:

- Name of the institution (e.g., university, hospital, foundation, school, etc.) conducting the research;
- Title of the research project and/or grant proposal in which the problem occurred;
- Name of the PI on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- A detailed description of the problem; and
- 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, educate the investigator, educate all research staff, suspend the protocol, suspend the investigator, conduct random audits of the investigator or all investigators, etc.)

Send OHRP email reports to: IRPT.OS@hhs.gov.

c. *Time Frame for Reporting Incidents*

The regulations require that reports must be submitted “promptly,” but do not specify the time frame for reporting. For serious incidents, this may mean reporting to OHRP within

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days. For a less serious incident, a few weeks may be sufficient. It may be appropriate to send an initial report, and indicate that a follow-up or final report will follow by the either:

- A specific date; or
- When an investigation has been completed or a corrective action plan has been implemented.

d. *Report Recipients*

Reportable events will be shared with government agencies, if applicable, and sponsors to the extent legally and contractually required, and with any others at the discretion of the IRB and the IO. The report may be sent to, or shared with, the following individuals and agencies:

- OHRP, when the research is subject to OHRP regulation;
- FDA, when the research is subject to FDA regulation;
- Funding agency, when funded by a government entity (e.g. Department of Defense, Education, and Justice require copies of such reports);
- Licensing and accrediting bodies, where the report or some portion thereof implicates the standards or regulations administered by those bodies;
- PI; and
- Internal entities managing the grant or contract or other research agreement.

e. *Reports & IRB Authorization Agreements*

If UCHealth IRB is serving as the IRB of Record for another organization according to an authorization agreement, then the UCHealth IRB will follow the agreed-upon terms in such agreement regarding reporting applicable events that occur at relying sites.

If UCHealth is relying on another IRB to serve as the IRB of Record according to an IRB authorization agreement, then the UCHealth IRB will receive a copy of any external reports made by the IRB of Record related to events that occurred at UCHealth. The IO will review the report and determine whether the UCHealth IRB will elect to submit its own additional report to the FDA, OHRP, or other regulatory agencies.

3. Noncompliance

a. *Communicating & Reporting Findings of Noncompliance*

In the event that the IRB makes a finding of noncompliance, the IRB will report such findings to the IO immediately. The IRB will coordinate with the IO to notify the Principal Investigator in writing of the findings of the convened IRB and any additional actions required in response to the findings, as well as notification of reporting to outside oversight

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agencies, if applicable. In addition, the IRB will coordinate with the IO to comply with any required reporting to outside oversight agencies (i.e. FDA or OHRP). All communications (letters, responses, etc.) that go to state or federal agencies related to human subjects research and the IRB must be approved by the IO prior to submission. Copies of communications with outside oversight agencies will be sent to the individual's supervisor (e.g. department head) and any appropriate internal UCHealth officials.

b. *Scientific Misconduct*

The IRB's responsibility is to protect the rights and welfare of research participants, which could be placed at risk if there is scientific misconduct on the part of the Principal Investigator or any member of the investigative team. It is, therefore, the duty of the IRB to be receptive to and act on good faith allegations of scientific misconduct. Allegations of misconduct in science must be communicated to the IO immediately.

REFERENCES

Guidance on Reporting Incidents to OHRP, dated June 20, 2011

FDA Reporting Requirements: Suspension or Termination of IRB Approval

OHRP Compliance Overview

21 C.F.R § 50.24

21 C.F.R. § 56.108

45 C.F.R. §§ 46.103

45 C.F.R. § 46.109(d)

VI. REVIEW OF RESEARCH

A. PRE-REVIEW

The IRB staff will conduct a pre-review of the protocol and all attachments. This includes submission of the application, informed consent, protocol, investigator's brochure (if applicable), and any recruitment materials. The elements of informed consent will be audited, and if essential criteria are missing, the IRB staff will request changes prior to submission to the IRB. These essential criteria include but are not limited to: federally required elements of consent, risk/benefit information, and the local informed consent requirements.

B. LIMITED REVIEW

Limited review is a process required for certain exemptions in 45 C.F.R. Part 46. In a limited IRB review, the IRB must determine that certain conditions are met but is not required to review all approval criteria in 45 C.F.R. § 46.111. Continuing review is not

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required for exempt research subject to a limited IRB review. Limited review does not apply to research subject to FDA regulations.

1. Expedited Review Process

Limited IRB review may be performed using the expedited review mechanism, that is, by the Chair or an experienced IRB member designated by the Chair (although it can also be conducted by the full IRB).

2. Research Not Subject to FDA Regulation

Limited IRB review does not apply to research subject to FDA regulations, which must undergo a full IRB review unless it is exempt under FDA regulations.

3. Continuing Review Not Required

When the IRB determines that the criteria for limited review is met, the research is exempt from other requirements in 45 C.F.R. Part 46, including continuing review.

4. Exemptions Requiring Limited IRB Review

Exempt categories are defined in Section VI.F. below.

a. Exempt Category 2

Exemption 2 is for research that only includes interactions involving educational tests, survey or interview procedures, or observation of public behavior if at least one of the three provisions included in this exemption is met. Limited IRB review is required only if the third provision of the exemption is being used—that the information obtained is recorded by the investigator such that the identity of the subjects can readily be ascertained either directly or through identifiers. For this provision of Exemption 2, the limited IRB review serves to determine that adequate provisions are in place to protect the privacy of subjects and maintain confidentiality of the data.

b. Exempt Category 3

Exemption 3 is for research involving benign behavioral interventions in conjunction with specified data collection methods if the criteria listed in one of three possible provisions are met. Limited IRB review is required only if the third provision of the exemption is being used— that the information obtained is recorded by the investigator such that the identity of the subject can readily be ascertained either directly or through identifiers. For this provision of

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Exemption 3, the limited IRB review serves to determine that adequate provisions are in place to protect the privacy of subjects and maintain confidentiality of the data.

c. Exempt Category 7

Exemption 7 is for the storage and maintenance of identifiable private information or identifiable biospecimens for potential secondary research use for which broad consent is required. This exemption requires limited IRB review to determine the following:

i. All requirements for broad consent in 45 C.F.R. 46.116(d) are met;

ii. broad consent is appropriately documented or documentation of broad consent is appropriately waived; and

iii. there are adequate provisions in place to protect the privacy of subjects and maintain confidentiality of the data, if there will be a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained.

UCHealth is not implementing exemption 7 until further guidance regarding broad consent is provided by OHRP.

d. Exempt Category 8

Exemption 8 is for secondary research involving identifiable private information or identifiable biospecimens, for which broad consent is required. This exemption requires the IRB to determine through limited review that there are adequate provisions in place to protect the privacy of subjects and maintain confidentiality of the data, and that the research to be conducted is within the scope of the broad consent obtained.

Note: UCHealth is not implementing exemption 8 until further guidance regarding broad consent is provided by OHRP.

REFERENCES

45 C.F.R. 46.104(d)(2)(iii)

45 C.F.R. 46.104(d)(3)(i)(C)

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45 C.F.R. 46.104(d)(7)

45 C.F.R. 46.104(d)(8)(iii)

OHRP Companion Q & As about the Revised Common Rule (August 20, 2018). https://www.hhs.gov/ohrp/sites/default/files/Revised-Common-Rule-Q%26As-08-20-2018.pdf

FDA Guidance: Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/impact-certain-provisions-revised-common-rule-fda-regulated-clinical-investigations

C. INITIAL REVIEW

All research proposals that intend to enroll human subjects must meet certain criteria before study-related procedures can be initiated. The criteria are based on the principles of justice, beneficence and autonomy as discussed in the Belmont Report and are specified below. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. In addition, certain other criteria that are specific to UCHealth may apply and must be met before any involvement of human participants may begin.

1. Local Concerns

The IRB will have the experience and expertise necessary to review and make determinations regarding the local research context. This may be achieved through:

- IRB member's personal familiarity of the local research context.
- A written review by a consultant(s) with knowledge of the local research context.
- A consultant may be invited to participate in the convened meeting discussion of the research proposal.

The IRB will review and confirm that the researchers are qualified to conduct research in the local context and are knowledgeable of local laws, regulations, customs, and practices. The IRB will seek the advice of legal counsel, as necessary. Local issues will be included in the IRB review during initial and continuing review.

The qualifications of the investigator will be verified by conditions of their employment or evidenced by the background stated on their vitae. Physician credentialing is completed by the medical staff credentialing process. Prior research experience or education is required. If there is no evidence of prior research education, it will be required prior to IRB approval.

2. Criteria for Approval

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In order to approve research covered by these regulations the IRB will determine that all of the following requirements are satisfied, in accordance with local, state and federal regulations:

- 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.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (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 IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR).
- Informed consent will be appropriately documented or appropriately waived.
- The research plan makes adequate provision for monitoring of subject safety. Minimizing risk as much as possible is our first priority.
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

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- When applicable, IRBs must determine that the additional protections of 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), or Subpart D (Additional Protections for Children Involved as Subjects in Research) of 45 C.F.R. Part 46 have been met. For additional information, refer to Section G. discussing vulnerable subjects.

IRB Members will also determine level of risk, the frequency of review for each protocol, monitoring of the investigative site, and whether third party assessment and follow-up will be needed. Members of the IRB vote upon the recommendations made by the primary reviewers according to the criteria for approval. All IRB members have full voting rights unless they have a conflict of interest. No one member's vote supersedes or is more important than another. All members who are present must establish a quorum.

3. Additional Criteria for Studies Involving PHI

Studies must include adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. All research conducted at UCHealth that creates, utilizes or shares PHI is subject to HIPAA regulations and conditions. UCHealth has designated the UCHealth IRB as the privacy board for HIPAA research authorization approval processes. All requests for HIPAA Authorizations and Waivers of Authorization for research purposes must be reviewed by the UCHealth IRB, unless an external privacy board has already provided its review of such requests, UCHealth IRB will not conduct a duplicative review of such requests. See Policy HIPAA in Research for more detailed information.

In order to proceed, one of the following must apply:

- Appropriate authorization is obtained from human subjects or their legal representative for the use or disclosure of their information;
- The UCHealth IRB, external IRB, or an external privacy board, has approved a waiver of such authorization;
- The PHI will be contained in a limited data set with appropriate safeguards to maintain privacy; or
- The PHI will be de-identified.

4. Device Research

If the protocol includes the use of an investigational device, additional risk determination is required. The convened IRB (or Chairperson if the review is expedited) will determine whether the study's test article presents a significant risk (SR) or a non-significant risk (NSR) of harm to study subjects. This assessment will be based on the information

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provided by the Principal Investigator and/or the Sponsor. The IRB's device risk determination must be documented in the IRB meeting minutes. Refer to Section VII.F.

If a Principal Investigator submits an NSR device research protocol that is determined by the IRB to be a significant risk device study, the Principal Investigator and FDA will be notified in writing. No further action will be taken by the IRB on the research until the sponsor or Principal investigator has met the requirements for an SR study described in 21 C.F.R. § 812.66 (Investigational Device Exemption regulations).

5. Review by Institution

Research must be aligned with the goals and values of UCHealth. Department approval is required prior to IRB review. The goal of approval is for both the IRB and the department to approve the research plan. Department officials may not approve research when the IRB has previously disapproved the project. Documentation of approval from the Director of the involved departments must be provided to the IRB upon application. Facility review is completed by the Director of Research Administration. Facility review findings should be communicated to the IRB.

6. Potential IRB Determinations

Guidance for Approval Criteria

HHS regulations define "IRB approval" as the IRB determination 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. The following procedures detail the requirements for approval and outline other IRB determinations when unable to approve a research protocol.

a. *Approve the Research*

When all required elements of approval are satisfied, the IRB will approve the protocol for a designated period of time based on a risk/benefit assessment.

- Approval will be determined by an action of the convened IRB. In the case of expedited review, the Chairperson or designee will grant approval.
- IRB approval may be withdrawn if the PI is non-compliant or if there is a safety risk to subjects.
- IRB approval may expire if a continuing approval (renewal) application is not submitted prior to expiration date.

i. Special Considerations Regarding Approval:

At the time of initial and continuing review the IRB will make a determination regarding the

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risks associated with the research protocols. Risks associated with the research will be classified as Minimal/Non-Significant or Significant. Examples for each include:

- Minimal/Non-Significant–-Risk associated with everyday life or examinations both physical and psychological that may be encountered during a yearly exam or educational activities.
    - Note: The Secretary's Advisory Committee on Human Research Protections (SACHRP) has described minimal risk as harms and discomforts ordinarily encountered. Minimal risk should reflect "background risks" that are familiar and part of the routine experience of life for the average person in the general population. It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population.
- Significant—Risk that involves the administration of investigational or experimental drugs (such as chemotherapy or cardiac medications) or surgical insertion of a medical device (such as a pacemaker, stent or hip prosthesis).

Meeting minutes will reflect the IRB's risk determination and the balance of risk as compared to benefit. Additional risk determination will also be made to fulfill obligations under Subpart B, C or D as appropriate when subjects require special protection or considerations. Please refer to Section F Significant and Non-Significant Risk.

ii. Period of Approval:

At the time of initial and continuing review, the IRB will make a determination regarding the frequency of the research protocol review. Protocols will be reviewed according to the degree of risk but no more than 364 days. In some instances, a shorter review interval may be required. Meeting minutes will reflect this approval period and any other stipulations they may require.

The decision to review a protocol more frequently than annually will be based on the risk of the protocol and/or the compliance history of the investigator.

Research that meets any of the following criteria may require review more than annually:

- The involvement of vulnerable populations likely to be subject to coercion.
    - For example: incarcerated minors, hospitalized psychiatric patients
- Phase 1 trials or investigations that require increased monitoring due to the nature of the design and the untested, uncertain effects of the test article or drug
- The probability or magnitude of anticipated risk to subjects is elevated
- Concerns about the experience of the Principle Investigator.
- Any other factors that the IRB determined relevant

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b. *Contingent Approval or Approval with Conditions*

Contingent approval, also known as approval with conditions, occurs when a convened IRB reviews and approves research but requires, as a condition of approval, minor modifications such as typos, several line editorial changes, additions to a protocol or any of the accompanying document(s), or additional documents. The convened IRB may approve research with conditions only if all of the criteria required for approval are satisfied, assuming the conditions are met. Contingent approval does not apply if substantive changes are required for the protocol to meet regulatory requirements. Substantive changes require further review by the IRB to determine whether all regulatory requirements for approval have been met. The content of the requested changes, as well as the terms of approval, will be voted upon during the IRB meeting.

The IRB may require the following as conditions of approval:

- Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g. confirmation that the research excludes children).
- Submission of additional documentation (e.g. certificate of CITI training).
- Precise language changes to protocol or informed consent documents

i. Investigator Notification and Timing of Deliverables

The Principal Investigator will be notified by letter about the required conditions of the approval. Protocols that are approved with conditions are reviewed each month as part of the "Old Business" part of the agenda. Submission of the change is expected in a timely manner from the receipt of notification, optimally within 30 days. If conditions have not been met after 6 months from the time of initial review, a full board review of the protocol may be required. If the Principal Investigator chooses not to submit any additional revisions or materials, the approval for the research activity would not become effective.

ii. Verification of Conditions of Approval

Verification that the required conditions have been met must occur before approval becomes effective. The verification process is typically started by the researcher submitting the required amended and/or additional documents for review and approval. The IRB Chairperson or their designee will review responsive materials from the Principal Investigator and determine that the conditions have been satisfied, and further review by the IRB at a subsequent convened meeting would not be necessary. Minor editorial changes that mirror the IRB request may be accepted by IRB staff. If deliverables are incomplete or further consultation is required, the amended protocol will be brought before the full board at the next convened IRB meeting.

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iii. Examples of how a contingency hold could be satisfied:

- Receipt of endorsement letter from a department director
- Correction of minor grammatical and typographical errors in the informed consent
- Investigator provides a copy of approved clinical privileges/hospital staff appointment
- Relocation of a statement in the informed consent document
- Addition of information to ensure that risks to subjects are minimized
- Addition of more information to improve the informed consent form process and/or to clarify precise agents and/or drug dosage levels
- Modification of the informed consent document to include the standard template
- Simplification of the description of study risks in the informed consent document to an 8th grade comprehension level

iv. Period of Approval

When the IRB approves a research study with one or more conditions, the date that all deliverables from the Principal Investigator are reviewed and accepted by the IRB chairperson or designee becomes the effective initial approval date. No research study activities may be initiated until the conditions have been satisfied.

c. *Tabled—Due To the Need for Revision or Clarification? (No Vote of Approval Taken)*

When an IRB reviews a research project at a convened meeting and is unable to approve the research, or the Principal Investigator does not present the research or is not available for IRB questions, the IRB may choose to table or defer approval. This happens when the IRB cannot make one or more determination required under 21 CFR 50.111 or 45 CFR 46.111 because significant details are missing or information is incomplete.

The IRB may require that the Principal Investigator make significant changes to the protocol or informed consent documents, or submit clarifications or additional documents prior to the next review.

If the IRB defers or tables a research project, the research may not proceed until the IRB reviews the revised research project and approves it at a subsequent convened meeting.

d. *Disapproval*

If the proposal fails to meet one or more criteria for IRB approval of research, the protocol will not be approved. This applies to both initial and continuing review of research and review of proposed changes to previously approved research.

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Disapproval of research can only be determined by majority vote at a convened meeting of the IRB. The proposal is allowed a subsequent review if substantive changes have been made by the investigator. A meeting with IRB members to explain the decision and requirements for approval may be requested by the Principal Investigator. No institutional official at UCHealth may override a disapproval action by the IRB.

REFERENCES

21 C.F.R. § 50.20

21 C.F.R. § 50.27

21 C.F.R. § 56.111

21 C.F.R. § 812.66

45 C.F.R. Part 46, Subparts B-D

45 C.F.R. § 46.102(h)

45 C.F.R. § 46.111

45 C.F.R. § 46.112

45 C.F.R. § 46.116

45 C.F.R. § 46.117

Mayo Clinic IRB Responsibilities for Local Context

OHRP Guidance on Engagement of Institutions in Human Subjects Research (October 16, 2008)

OHRP Frequently Asked Questions: Assurance of Process

OHRP Correspondence: Determining when institutions are engaged in research (January 13, 2009)

OHRP Guidance: Approval of Research with Conditions (November 10, 2010)

SACHRP letter to HHS Secretary: Recommendations related to waiver of informed consent and interpretation of “minimal risk” (January 31, 2008)

D. CONTINUING REVIEW

IRB has the authority to approve, suspend, or terminate approval of research that is not being conducted according to federal law or institutional policy. Approval is for no more than one year. Studies that are not renewed will have their approval expire.

IRB approval may be withdrawn at any time if warranted by the conduct of research (e.g. more than an expected number of adverse events, unexpected serious adverse events, or evidence that the investigator is not conducting the investigation in compliance with IRB and UCHealth guidelines).

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Periodic review throughout the year of all reported research activities is necessary to determine whether approval should be continued or withdrawn. The regulations authorize the IRB to establish procedures for the concurrent monitoring of research activities involving human subjects. In accordance with HHS regulations, continuing review by the convened IRB with recorded vote on each study is required, except as described below.

All non-exempt research involving human participants must be reviewed at least once per year. Approval is effective for no more than one year. Studies that are not renewed will have their approval expire. No research-related activities, including new subject enrollment, may occur after the protocol expiration date unless the IRB determines that it is in the best interests of participants to continue during the lapse in IRB approval. Investigators must apply for renewal of a study in writing no less than 60 days in advance of the expiration date. Renewal forms can be obtained in the IRBManager electronic database.

1. Continuing Review Exceptions

All research subject to FDA regulations must have continuing review. Research that is not regulated by FDA and meets one of the following does not require continuing review:

(i) Research eligible for expedited review in accordance with 45 CFR 46.110 (see Section VI. D.);

(ii) Exempt research conditioned on limited IRB review (under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8)).

(iii) Research that has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care (i.e., all interventions are complete).

The IRB may choose to require continuing review, as long as the IRB documents the decision and the rationale for this decision.

2. Procedures for Continuing Review

Key procedures for continuing review are the same as initial approval procedures. Please refer to Section V – Functions and Operations, Section c – Initial Review, Section D –

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Continuing Review, Section E– Expedited Review, Section G – Vulnerable Populations, Section F – Significant and Non-Significant Risk, Section VIII – Informed Consent, and Section IX – Responsibility of Investigators.

A quorum must be present for vote of approval. No conflicting interest may exist for participating members. Documentation must delineate votes, key actions, and resolution of controverted issues. This section summarizes the elements the IRB must take into account for continuing review.

3. Criteria for Renewal

Continuing review must be substantive and meaningful. The IRB must confirm that all information provided is consistent with previous approval. It may be that, only after research has begun, the real risks can be evaluated. The preliminary risk/benefit profile can be evaluated to the actual risk/benefit ratio. The IRB can then determine whether or not the study can be renewed at the same risk/benefit ratio, or if new information has changed that determination.

Therefore, the IRB must determine that the research plan includes:

- The risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits and the knowledge expected to result;
- The selection of subjects continues to be reasonable in relation to anticipated benefits;
- Selection of subjects is equitable;
- Informed consent process will be completed for every subject or LAR (legally authorized representative), and appropriately documented;
- Provisions for monitoring data collected to ensure the safety of subjects remain adequate;
- Protections to ensure the privacy of subjects and confidentiality of data remain valid;
- Appropriate safeguards for vulnerable populations are included as applicable;
- Study enrollment should be evaluated, as well as accrual rates;
- Subject withdrawals are evaluated based on the number, issues, summary or reasons for local withdrawals.

Once the IRB determines that the previously approved research satisfies the above criteria, its focus should shift to any new information that the investigator has provided. The IRB should determine if new information has revised the protocol and subsequently altered the above criteria, particularly in areas of risk, safety, and adequacy of obtaining informed consent, investigator and/or site issues and the progress of research.

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4. Risk Assessment and Monitoring

One of the most important considerations for the IRB at the time of continuing review is whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to the subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result. The IRB's continuing review procedures should ensure that the IRB will consider relevant information received since the date of the last IRB review and approval of the research project from the investigator, any monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, a data and safety monitoring board (DSMB), or a data monitoring committee (DMSC)), or any other source. Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review regarding the risk:/benefit relationship of the research.

5. Documentation For Renewal Approval

In order to determine whether a study will be renewed, IRB members will revisit the documents listed below. If the IRB or IRB staff determines that the submitted documents are not adequate, investigators will be required to submit additional information. The investigator may be contacted or their presence required at the convened meeting for answering questions or explaining the details of the study. If IRB staff has determined that the submission materials are adequate, then the study is added to the next agenda and submitted to reviewers.

The minutes of the IRB meetings will document separate deliberations, actions and votes for each protocol, and the portion of the protocol (e.g. amendments) undergoing continuing review. Principal Investigators will be sent a report (in writing) regarding the actions taken by the IRB and subsequent required PI actions. It will include deadlines as appropriate regarding renewal and continued review. The stamped approval and expiration dates will appear in the footer/header (if space allows) of the approved Informed Consent Form. Documentation should show that the IRB reviewed the most recent study materials and that all waiver criteria has been met.

a. *Progress Report (Renewal Form)*

All appropriate documentation (e.g. protocol and consent form) must accompany the continuing review application. Interim findings, relevant recent literature or modifications since the last renewal should be included in this summary.

All IRB members shall receive a renewal form that will serve as the "progress report" prepared and submitted by the Principal Investigator. It will include the total number of subjects to date, new accruals and comparison to anticipated accrual numbers in original application.

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The progress report shall summarize:

- Deviations;
- Related adverse event experiences;
- Any unanticipated problems involving risk to subjects or others;
- Any withdrawal of subjects or complaints about the research since last review;
- Amendments and changes to a research protocol should be submitted as they occur during the course of the study (Changes should be summarized at the time of continuing review); and

The most current Informed Consent should be submitted if the study is open to accrual. For example:

- Accrual Closure – Active Patients: If the study is closed to accrual and subjects are in active treatment, a consent form must be submitted to the IRB.
- Accrual Closure – Long-Term Follow-Up Only: If the study is closed to accrual and subjects have finished all active treatment, a consent form and protocol does not need to be submitted to the IRB.
- Accepting Transfer Patient After Local Accrual Closure: When a patient transfers from another study site and requires treatment and/or follow-up, the most current informed consent form should be obtained from the sponsor and submitted for approval. An amendment may need to be submitted to re-open accrual and/or increase accrual if accepting the transfer patient will put accrual over the local approved amount.

Other relevant reports may include:

- Sponsor Annual Reports;
- Notification of any additional personnel changes; and
- Data Safety Committee reports and/or any aggregated information about regulatory actions, safety and risk assessments, recalls or device disposition.
- The Investigator's Brochure.

b. ***Current Approved Protocol***

The current approved protocol, along with any amendments since the initial review, should be submitted. Amendments to a protocol should be submitted on an ongoing basis throughout the course of the study.

c. ***Consent Document and Adequacy of Process***

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Members shall review the most current consent document and ensure that the information is still accurate and complete addressing the required elements; i.e. risk/benefit and/or alternative procedures. The IRB will review the content to be sure that all current information is included. The most current information should allow the subject to determine if they want to continue participation. Any information regarding the process of informed consent should also be evaluated.

If a waiver of consent has been granted initially, verification that risks remain minimal and conditions unchanged are required to renew the waiver determination. Likewise, if the IRB waived the requirement for documentation of consent for some or all subjects, then the IRB should assess the accuracy of the content of the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects.

d. *Data Safety Monitoring Boards (DSMB)*

A Data Safety Monitoring Board (DSMB) report may be useful in assessing risk and safety of a clinical trial. A DSMB's responsibilities include review of all adverse events from all sites, interim findings and relevant literature (e.g., DSMB's operating in accordance with the National Cancer Institute Policy for Data and Safety Monitoring of Clinical Trials). The IRB will rely on a current statement from the DSMB (when available) indicating that it has reviewed the protocol for safety. Any new information will be evaluated to ensure that previous provisions for safety are still in effect. A summary of DSMB findings will be provided as part of the continuing review application.

e. *Recruitment and/or Other Patient Materials*

All materials that are viewed or reviewed with the patients must be approved by the IRB. This includes recruitment materials, advertisements, educational materials, brochures, pamphlets and scripts. These documents do not need to be resubmitted with the renewal unless changes were made.

6. Special Considerations for Continued Review

Unless the research is subject to one of the continuing review exceptions (see Section D.1. above), continuing IRB review is required as long as individually identifiable data is collected on enrolled subjects. There are no continuing review exceptions for research regulated by FDA.

a. *Accrual Closure*

If the study is closed to accrual and subjects are in active treatment, a consent form must be submitted to the IRB. If the study is closed to accrual and subjects have finished all active treatment, a consent form and protocol does not need to be submitted to the IRB.

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When a patient transfers from another study site and requires treatment and/or follow-up, the most current informed consent form should be obtained from the sponsor and submitted for approval. An amendment may need to be submitted if accepting the transfer patient will put accrual over the local approved amount.

b. ***Local Concerns Regarding the Investigator and/or the Site***

Local issues will be included in the IRB review during initial and continuing review. These local issues include:

- Changes to the investigators' situation, qualifications and/or credentials;
- Complaints from any source related to research including evaluation, investigation and resolution;
- Changes in institutional commitment for the project;
- Reports from third parties;
- History of protocol deviations, unanticipated problems and serious adverse events;
- Investigator concerns about the trial at the local site, including inability of subjects to understand the Informed Consent and study coordinator performance; and
- Waiver requests and determinations.

c. ***Total Subject Enrollment***

As part of its initial review of a research project, the IRB typically will have approved a protocol that includes the expected total number of subjects to be enrolled by the investigator. Evaluating information about the number of subjects enrolled in the research at the time of continuing review may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. A marked difference between the actual and expected enrollment may indicate a problem with the research project that requires further evaluation. This may include whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed.

d. ***Subject Withdrawals***

Subjects may discontinue their participation in research at any point for various reasons (e.g., serious adverse events, conflicts with the investigators, transportation problems, etc.).

The IRB's continuing review procedures in general should provide for review of:

- The number of subjects who discontinued their participation; and
- A summary of the reasons for the withdrawals, if known.

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IRB review of this information may shed light on problems related to the conduct of the research. For example, a high rate of subject withdrawal secondary to serious adverse events may indicate that the risks of the research are greater than expected. This may lead the IRB to conclude that the research should not be approved for continuation because the risks to subjects are not being minimized, or are not reasonable in relation to the anticipated benefits to the subjects.

7. IRB Continuing Review Process

a. *Involvement of IRB Staff in Preliminary Review*

Appropriately trained IRB staff members may perform preliminary assessments of continuing review documents to facilitate the continuing review of research by the IRB members. As part of this preliminary assessment, IRB staff may perform the following functions, among other administrative tasks:

- Confirm that all documents required by the IRB have been submitted by the investigator;
- Assess whether the information and documents are consistent with the research protocol previously approved by the IRB;
- Confirm that the informed consent document submitted by the investigator matches the current IRB-approved informed consent document;
- Aid the IRB in identifying important issues and concerns that the IRB may wish to consider; and
- Provide technical assistance and guidance to the IRB at convened meetings and to the IRB Chairperson or designated IRB member(s) during an expedited review process.

IRB staff members who are not IRB members may not be delegated responsibility for making the determinations that must be made by the IRB at the time of continuing review and may not approve research on behalf of the IRB.

b. *Determining Which Studies Require Review More Frequently Than Annually*

The IRB must conduct continuing review of protocols for purposes of renewal at intervals appropriate to the degree of risk, which is determined at the initial review, but not less than once per year. “Not less than once per year" means that the research must be reviewed on or before the first anniversary of the previous IRB review date.

The IRB must consider whether the current frequency of continuing review is appropriate. If risks posed to subjects have increased significantly, or if there is a history of problems or noncompliance, then the IRB will reapprove a project for a shorter timeframe. For example, the IRB may approve a study for six months (after determining that the approval

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criteria are satisfied), or the IRB may stipulate that IRB review must occur after a defined number of participants have been enrolled. Research that meets the criteria for more frequent than annual review may or may not require that same level of monitoring in subsequent years.

The IRB may require mandated (condition of approval) monthly patient status reports for Phase I or Phase II studies with higher risks or if vulnerable populations are included. The PI will need to submit the monthly patient status report for each patient while they are in active treatment. These monthly reports are required to be submitted prior to the packet submission deadline each month. In the event that no patients are on active treatment, the PI will send an email to the IRB office to notify them that no report is required for the month.

c. *No Extensions of Approval Period*

There is no grace period extending the approval of the research beyond the expiration date. Extensions beyond the expiration date will not be granted. The continuing review request report should be filed approximately 30-60 days before the study approval period ends to allow enough time for approval and avoid expiration.

If the researcher does not contact the IRB, the study's approval will expire on the anniversary date. During the time of protocol expiration, no new subjects can be enrolled. No research data may be collected and no procedures that are performed for the purposes of the protocol may continue or be initiated until the continuing review application is reviewed and approved. Expiration of IRB approval is not required to be reported to OHRP unless serious noncompliance surrounds the expiration.

The IRB will address on a case-by-case basis, situations in which protocol expiration would seriously jeopardize safety or well-being of an individual. IRB approval is required to continue protocol-associated medical care beyond the expiration date. This determination will be based on subject welfare and not for the ease of the researcher.

When IRB approval lapses and the PI wants to continue the study, the IRB will complete the continuing review as soon as possible, which may be at the next scheduled convened IRB meeting. The IRB will document the reason for the occurrence of the lapse and identify steps to be taken to prevent future lapses. A new anniversary date for expiration may be established.

8. Site Visits

The informed consent process may be observed by the IRB or a third party. This observation is meant to verify that the study is being conducted as required by site-specific policies and procedures as appropriate. Investigators may be asked to submit copies of signed informed consent forms or other documents to ensure their compliance with IRB requirements. The IRB may conduct interviews with screened and/or enrolled subjects as necessary.

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IRB staff or IRB members may perform site visits or use another party, either affiliated or not with the institution, to verify information in the study application, or in any interim or continuing review submissions. The criteria for selecting Investigators to be visited may include:

- Studies that involve a potential high risk to subjects such as Phase 1 or "Investigator as Sponsor" protocols;
- Studies that involve vulnerable populations or new populations of subjects;
- Studies that involve large numbers of subjects or multiple sites;
- Novice investigators to research that require more supervision;
- Investigators who have shown an increase in deviations, adverse events, patient withdrawals or non-compliance issues in the past;
- Studies requiring auditing of medication use and/or storage;
- Investigators who have a history of noncompliance related to continuing review within the last three years;
- Information provided by the investigator is inconsistent with other information known to the IRB, and the inconsistency cannot be resolved through communication with the investigator; or
- Any other reason the IRB believes verification should be required.

9. Reports from Employees, Staff and Faculty

It is the responsibility of IRB staff and IRB members to investigate and act on information or reports received from any source. If a study is being conducted in a way that could adversely affect the rights and welfare of research subjects, it will be investigated. Third party verification may come from UCHealth nurses, purchasing agents, or physician peers. Their information may support that no material changes have occurred. Sponsors and Investigators are asked to submit copies of monitoring reports, federal communications such as audit reports and reviews by other collaborating IRBs. The IRB will review the independently verified information and may require protocol modifications, contingencies or investigator conditions prior to granting continuing review approval.

10. Review of Oversight/Monitoring Reports and Findings

For studies that operate with a monitoring plan that includes oversight by a DSMB or equivalent (DMC, DRC, DSMC, etc.), the IRB requires copies of reports to be submitted at the time of original receipt from that entity. Submission of these reports may result in follow-up correspondence or official submissions to ensure compliance with the DSMB recommendations.

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Additionally, for biomedical research that carries greater than minimal risk, study teams are required to submit a monitoring summary with their continuing review that provides an assessment of the outcomes of the approved plan for monitoring/auditing that occurred during the approval year.

11. Non-Compliance Reporting

Non-compliance can result from deviating from a protocol, not adhering to IRB requirements, or putting participants at risk. All credible reports of inappropriate involvement of human subjects in research must be provided to the IO and investigated by the IO, Director of IRB Administration, and members of the IRB. For more details, see Research Misconduct and Research Non-Compliance Policies.

12. Significant New Findings

During the course of a study, the IRB may review reports generated from a DSMB, adverse event reports, current literature, and other sources to determine the risk status of the study and whether or not the risk/benefit balance is still acceptable. The IRB will determine if new information needs to be conveyed to subjects. The consent form will be updated with such findings.

13. Modifications

Changes in approved research may not be initiated without prior IRB review (full or expedited review, as appropriate) except where necessary to eliminate immediate hazards to human subjects. Investigators or sponsors must submit requests for changes to the IRB in writing. Upon receipt of the protocol change, an IRB Member will determine the risk categorization of the revision. If the change represents more than a minimal risk to subjects, it must be reviewed and approved by the convened IRB. Minor changes, involving no more than minimal risk to the subject, will be reviewed by the expedited review procedure.

The IRB categorizes modifications into three types: Amendments, Deviations, and Exceptions that require reporting to the IRB:

a. *Amendments*

An amendment is a permanent, intentional action or process that revises/amends/modifies a previously adopted research protocol. Amendments should be submitted concurrently when they are posted by the sponsor. Brief amendment summaries should be submitted at the time of renewal as a reminder to the IRB of previously approved amendments during the year.

Information relating to protocol amendments will be provided to research participants when the information may relate to their willingness to continue to be a part of the

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research. Upon receipt of the protocol amendment, the IRB administrator will determine the appropriate level of review.

Minor modifications are changes that do not materially affect an assessment of the risks and benefits of the study, and do not substantially change the specific aim or design of the study. Examples of minor modifications may include narrowing the inclusion or exclusion criteria, changes to the dosage form (when the dose and administration remain consistent), an increase in the number of study visits, the addition or deletion of study sites, or the addition or deletion of qualified investigators.

b. *Exceptions*

An exception is a prospective, one-time, intentional action or process that departs from the IRB-approved study protocol, intended for a single occurrence. Investigators must submit a request for approval of exception before the exception occurs. Upon receipt of an exception request, the IRB administrator determines the appropriate level of review. The level of required review is based on the following factors:

- time sensitivity
- level of risk in both the study and the alteration
- whether the change is in the best interest of the participant
- whether the change has the prospect of directly benefiting the participant
- whether the risk/benefit ratio of the change is in the patient's favor

Exception requests that present no more than minimal harm to the participant is eligible for expedited review. Expedited review may also be available for exception requests that pose more than minimal risk, but (a) the request is time-sensitive, (b) the exception is in the participant's best interests or the prospect of a direct benefit exists, and (c) the risk/benefit ratio of the exception favors the participant.

If the exception request presents more than minimal harm to participants and one of the following factors apply, then the request will require convened IRB review:

- It is unclear whether the exception is in the participant's best interests or whether the prospect of a direct benefit is present;
- It is unclear whether the risk/benefit ratio favors the participant; and
- The request is not time-sensitive and there is sufficient time to allow convened IRB review to occur.

When the IRB reviews exceptions, it will determine whether information related to the changes should be provided to participants if it would affect their willingness to continue to participate in the research. The IRB may require supplemental information, such as an addendum consent form, telephone script, or participant letter.

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c. *Deviations*

Deviations are generally unintentional actions or processes that depart from IRB approval and are identified retrospectively. Deviations must be reported by the Investigator to the IRB within five business days after discovery if one or more participants were potentially placed at increased risk of harm, if the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

When the IRB reviews deviations, it will determine whether information related to the changes should be provided to participants if it would affect their willingness to continue to participate in the research. The IRB may require supplemental information, such as an addendum consent form, telephone script, or participant letter.

14. Reportable Events

Ensuring subject safety is of the greatest importance for the IRB and is a primary goal of the clinical study. Reports of any unanticipated problems involving risks to human subjects or others ("Unanticipated Problems") must be promptly submitted to the IRB (21 C.F.R. 56.108(b)(1) and 45 C.F.R. 46.108(a)(4)(i)).

An **Unanticipated Problem** is any event, incident, experience or outcome that, in the opinion of the investigator, is:

1) Unexpected,
2) Related or possibly related to the research, and
3) Suggests that the research places subjects or others at greater risk of harm.

Events that meet the criteria of an Unanticipated Problems generally require consideration of substantive changes in the research protocol, informed consent process or other corrective actions to protect the safety, welfare, or rights of subjects or others. have implications for the Study (see OHRP "Unanticipated Problems Involving Risks & Adverse Events" Guidance, 2007). Examples of actions or changes that may need to be considered in response to an Unanticipated Problem include:

- Changes to the protocol by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- Modification of inclusion or exclusion criteria to mitigate the newly defined risks;
- Implementation of additional procedures for monitoring subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedures in currently enrolled subjects;

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- Modification of informed consent documents to include a description of newly recognized risks; and
- Providing additional information about newly recognized risks to previously enrolled subjects.

Investigators must submit reports within ten (10) business days of the time the Unanticipated Problem becomes known to the study team except in the case of adverse events, which must be submitted within five (5) business days. Adverse events that involve an unforeseen death must be reported within three (3) business days.

a. *Adverse Events*

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, that is temporally associated with the subject's participation in the research (OHRP Guidance, 2007). Only adverse events that meet the criteria of an Unanticipated Problem must be reported to the IRB. Most adverse events are not Unanticipated Problems and do not have to be reported. Known or foreseeable risks associated with the procedures involved in the research that are, for example, described in the protocol and related study documents such as an investigator's brochure or the IRB-approved informed consent document are not Unanticipated Problems.

Adverse events that must be reported to the IRB include the following:

- Any serious adverse event (regardless of whether the event is on-site or off-site) that occurs any time during or after the research study, which in the opinion of the PI, is both unexpected and related to research procedures.
- Unanticipated adverse device effect—any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device (if the effect or problem was not identified in nature or severity in the investigational plan), or any unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Reports will be reviewed by the IRB Chairperson or designee. If the IRB Chairperson determines that action may be needed to protect the safety of research subjects because of the nature or frequency of reported adverse events, he/she may take such action immediately. If there are immediate safety concerns to local subjects, the IRB Chairperson will temporarily suspend research activity, pending full review by the convened IRB. No new subjects may be enrolled in the temporarily suspended study, and accrual is temporarily suspended during the time in-between investigator notification to sponsor, IRB review, and approval of an action plan.

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The IRB or designated subcommittee will review summaries of all pertinent safety reports and serious adverse events as soon as possible and develop the need for an action plan by the investigator to report at the next convened meeting. Accrual may resume as directed once the action plan has been approved or as directed at the IRB meeting. Details of reporting and IRB review with risk determination are detailed in the UCHealth Guidance Unanticipated Problems and Adverse Events.

b. ***Other Unanticipated Problems***

Some events, incidents, experiences, and outcomes are Unanticipated Problems but do not meet the definition of an adverse event. Unanticipated problems that are not adverse events include any unforeseen events that involve risks (including risks of social or economic harm) or affect the safety or welfare of subjects or others, or have an effect on the integrity of the research. Examples of Unanticipated Problems that are not adverse events include, but are not limited to:

- Withdrawal from marketing for safety concerns of a drug, device or biologic used in a research protocol;
- Intentional change to a protocol taken without prior IRB review to eliminate apparent immediate hazard to research participant;
- Deviations—meaning an accidental or unintentional change to the IRB-approved protocol—that placed one or more participants at increased risk, has the potential to reoccur, or has the potential to qualify as serious or continuing noncompliance;
- Breach of confidentiality;
- Incarceration of a participant when the research was not previously approved for prisoners and the investigator believes it is in the subject's best interest to remain in the study; and
- Premature completion of the study.
- Loss of data as a result of a stolen laptop;
- Reports of adverse events, subject drop-outs, or protocol deviations that are occurring at higher than expected rates;
- Loss of multiple staff members;
- Injury to a staff member while conducting study-related procedures;
- Medication administration errors; and
- Reports and other information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency (e.g. lower response to treatment, more severe side effects, a paper is published from another study that shows that an arm of the research study is of no therapeutic value, etc.).

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Unanticipated Problems involving risk will be the IRB's highest priority for review, advice, and action. Unanticipated Problems should be reported as they occur. A yearly summary is included as part of the continuing review application. Determination of whether an action plan is required or accrual requires suspension is made immediately upon notification. Reporting to federal agencies will be part of the required action plan if related risk is determined to be increased for others both locally and nationally.

c. ***IRB Review of Reports***

If a reportable event occurs, the investigator must submit a report describing the event. The IRB Chairperson or their designee will conduct an initial review of reportable events. If the IRB Chairperson or designee determines that a reported event does not meet reporting criteria, or is determined to carry no more than minimal risk, then the reports will be summarized at the time of continuing review and IRB members will review such events in the aggregate and comment, if necessary.

If a reported event requires review at a convened meeting, then a primary reviewer will be assigned to review the sponsor protocol, investigator brochure, original IRB application form, consent document, event summary, and any other supplemental information. IRB members will have access to the original application form, consent document, event summary and any other necessary information. The IRB may request a consultant opinion or engage the department chair or director if additional information is necessary.

d. ***IRB Actions Based on Reportable Events***

When determining whether an event qualifies as an unanticipated problem requiring external reporting, the IRB uses the following criteria:

- Was the event unexpected in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents and (b) the characteristics of the subject population being studied?
- Was the event related or possibly related to participation in the research? ("Possibly related" means that there is a reasonable possibility that the event may have been caused by the research procedures.)
- Does the event suggest that the research places subjects or others at a greater risk of physical, psychological, economic, or social harm than was previously known or recognized?

After reviewing a report, the IRB may take the following actions:

- Accept the report with no additional requirements;
- Approve the investigator's proposed changes;
- Administrative hold on the study pending IRB receipt of further information;
- Require modification of the protocol;

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- Modification of the information disclosed during the consent process;
- Provide additional information to current participants if the information may relate to the participant's willingness continue participation;
- Make arrangements for clinical care outside the research or additional follow-up for participants;
- Provide additional information to past participants;
- Require current participants to re-consent to participation;
- Observation of the research or consent process;
- Require additional training of the investigator;
- Notification of investigators at other sites;
- Obtain additional information; or
- Termination of the research.

15. Possible Outcomes of Continuing Review

Assessment of safety is the highest priority for the IRB. Reviews of research should be an ongoing process for the IRB. Significant changes to the protocol require immediate notification to the IRB and should not wait until renewal time.

As an outcome of continuing review, the IRB may:

- Authorize continuation of the research;
- Require that the research be modified or halted altogether;
- Impose special precautions; or
- Relax special requirements it had previously imposed.

Any changes required to obtain continued renewal approval shall be provided to the investigators by the IRB staff.

a. *Suspension or Termination of IRB Approval of Research*

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with: IRB policies, federal regulations, or has been associated with unexpected serious harm to subjects. The investigator may be allowed to make modifications and reapply for approval if all safety concerns have been mitigated. No institutional entity may overrule a study termination determination. If there is a pattern of non-compliance with the requirements for continuing review, the IRB may need to take corrective action. Federal reporting would be required for serious and/or continuing non-compliance.

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IRB approval may be withdrawn at any time for the following reasons:

- If the risks to the subjects are determined to be unreasonably high;
- When adverse events or unexpected problems occur at an accelerated rate;
- If the investigator is not conducting the protocol in compliance with IRB or federal guidelines.

Such findings may result in more intensive review (such as on-site audit) following temporary suspension of the study to determine if approval should be withdrawn or enrollment stopped until corrective measures can be taken or the study terminated. Procedures for withdrawal of enrolled subjects will consider the rights and welfare of subjects. Subjects will be informed immediately of the suspension.

A decision to suspend or terminate a protocol must include an explicit consideration for the rights and welfare of participants already enrolled in the study. If suspension or termination is imposed on an investigator, the IRB Chairperson may be consulted about whether and how to continue the care of enrolled participants. The matter will be discussed at the next convened IRB meeting.

Any suspensions or terminations will include a statement of the reasons for the IRB's action and shall be promptly reported by the IRB to the investigator, any appropriate compliance offices, and the IO. The timeframe for notification will depend on the urgency of the matter. Situations presenting immediate, unforeseen risk to participants will be reported immediately to the IO and sponsors. When the research is sponsored by HHS, the IO or an authorized designee will notify OHRP. For FDA-regulated research, the IO or an authorized designee, will notify FDA in writing after the IRB has made a final determination.

Enrolled participants will be notified if a protocol in which they are enrolled is suspended or terminated. The IRB will determine at a convened meeting how and when the notification will take place. The IRB will consider whether former participants must be notified.

If the UCHealth IRB is servicing as the IRB of Record for external organizations through an IRB authorization agreement, the IRBs at the relying organizations will be promptly notified of any decision to suspend or terminate the protocol.

16. Re-consenting Participants Due to Amendment or Significant New Information

When the IRB determines that participants should be re-consented following amendment approval, the method of subject notification is determined by level of risk.

a. *Risk Change*

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Re-consenting is mandated, when an amendment increases the overall risk of the protocol or contains information that could affect the subject's willingness to participate. The re-consent process should include a face-to-face interaction requiring a signed informed consent form. Suspension of further accrual may be required between the initial notification and IRB approval of the action plan.

b. ***Urgency***

Telephone notification may be used to notify subjects quickly regarding urgent changes involving risk. This verbal notification must be followed by a face-to-face interaction with written documentation of informed consent form at the next research visit.

c. ***No Risk Change***

The subject can be notified by letter or secured email or fax for changes in the protocol or Informed Consent without risk. If letter/email/fax notification is used, the return of signed documents or acknowledgement is required. This method is recommended to prevent subjects from making a special trip for protocol notifications. Letter notification may be helpful for sharing new information, newsletters, appointment cards, and other subject materials not involving risk.

REFERENCES

OHRP Guidance on IRB Continuing Review of Research (November 10, 2010)

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

OHRP IRB Review of Protocol and Informed Consent Changes in Cooperative Group Protocols (OHRP Memo to the National Cancer Institute, 2008); 9-29-2008. Downloaded 3-9-2018

SWOG Memorandum of March 20, 2008 regarding OHRP Regulations on Changes in Clinical Trial Informed Consent Documents and Continued Enrollment of New Participants. Downloaded 3-9-2018

FDA IRB Continuing Review After Clinical Investigation Approval (February 2012)

21 C.F.R. § 56.103(a)

21 C.F.R. § 56.108(a)(4)

21 C.F.R. § 56.113

21 C.F.R. § 812.150 (b)(6)

45 C.F.R. § 46.103(b)(4)

45 C.F.R. § 46.108(b)

45 C.F.R. § 46.109

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45 C.F.R. § 46.115 (a)(2)

E. EXPEDITED REVIEW

An expedited review procedure is a review of research by the IRB Chairperson and/or an IRB Member designated by the Chairperson. When reviewing research under an expedited procedure, the IRB Chairperson or designated IRB Member will receive and review all the documentation required. The IRB may use the expedited review procedure to review any of the following types of research:

- Involves only procedures listed in one or more of the specific categories listed in the regulations and involves no more than minimal risk. (See expedited research categories below.)
- Minor changes in approved research during the period for which approval is authorized.
- Limited IRB review is a condition of exemption (see Section VI. B.4. above) and the research is not regulated by FDA.

This policy applies to both initial and continuing IRB review.

1. Definition of Minimal Risk

Minimal risk exists when "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." Minimal risk includes as harms and discomforts ordinarily encountered and should reflect "background risks" that are familiar and part of the routine experience of life for the average person in the general population. It should not be based on those harms and discomforts ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population.

2. When Expedited Review May Not Be Used

The expedited review procedure may not be used when 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. In this situation, reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

3. Expedited Review Research Categories

Inclusion on this list 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. Expedited Categories 1 through 7 below apply

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to initial and continuing review. Expedited Categories 8 and 9, require full initial review but are eligible for expedited continuing review.

a. Federal Research Categories for Expedited Initial and Continuing Review

Expedited Category 1:

- Clinical studies of drugs and medical devices only when (a) a new drug or device application is *not* required; and (b) the device is cleared/approved for marketing and the medical device is being used according to its cleared/approved labeling.
- Research on drugs for which an investigational new drug application is **not** required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- Research on medical devices for which –
    - An investigational device exemption application is **not** required; or
    - The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Expedited Category 2:

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

Expedited Category 3:

- Prospective collection of biological specimens for research purposes by noninvasive means. Examples include:
    - Hair and nail clippings in a non-disfiguring manner;
    - Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

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- Permanent teeth if routine patient care indicates a need for extraction;
- Excreta and external secretions (including sweat);
- Un-cannulated saliva collected either in an un-stimulated fashion or stimulated by chewing gum-base or wax or by applying a dilute citric solution to the tongue;
- Placenta removed at delivery;
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
- Supra- and sub-gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
- Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
- Sputum collected after saline mist nebulization.

Expedited Category 4:

- Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples include:
  - 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;
  - Weighting or testing sensory acuity;
  - Magnetic resonance imaging;
  - Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
  - Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate, given the age, weight, and health of the individual.

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Expedited Category 5:

- Research involving materials (data documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis.) (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)

Expedited Category 6:

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

Expedited Category 7:

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

b. ***Federal Research Categories for Expedited Continuing Review Only***

Expedited Category 8:

- Continuing review of research previously approved by the convened IRB may be approved through an expedited process as follows:
    - 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
    - Where no subjects have been enrolled and no additional risks have been identified; or
    - Where the remaining research activities are limited to data analysis.

    Note: Continuing review is not required for research in this category if it is not subject to FDA regulation.

Expedited Category 9:

- Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through

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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.

4. Authority of the Expedited Reviewer

The Chairperson, Vice-Chairperson, or other experienced IRB Member, as designated in writing by the IO or by the IRB Members voting in a convened meeting (the "Expedited Reviewer") will conduct the expedited review and, after appropriate opportunity for discussion at a convened IRB review, will document his/her recommended determination of the applicable expedited review category in accordance with Section 6 below. The Expedited Reviewer may not disapprove the research by his/her primary expedited review. A research proposal may be disapproved only after review by the convened IRB. Consultants may assist the IRB in the review of issues that require additional expertise, but the consultant may not carry out the expedited review.

5. Notification of the IRB

When the expedited review procedure is used, all regular IRB members will be informed of considerations made by the Expedited Reviewer at the next convened meeting. The IRB members will receive electronic documents for review as necessary and will be given an opportunity to ask questions or raise concerns with any component of the expedited review.

6. Documentation

The information provided to the Expedited Reviewer for expedited review is the same information that a primary reviewer receives for review at a convened meeting. If the study qualifies for expedited review, the Expedited Reviewer will document his/her recommended determination of the applicable expedited review category. The Expedited Reviewer will consider all of the criteria considered for convened IRB review.

The minutes will include documentation of the studies that were reviewed via expedited review and any issues and resolutions relating to questions that IRB members had concerning the research reviewed.

7. Additional Items That May Be Reviewed By the Chairperson or Designee

Conditional or contingent approval pending minor revisions or requests for clarification may be approved by the expedited process. Revisions to consent documents and other documentation or clarifications submitted as a result of full IRB review and as a condition to final approval may be reviewed by the Expedited Reviewer. Final approval will be issued providing the revisions, documentation, or clarifications do not indicate or result in a change to the study risk/benefit profile.

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The IRB Regulatory Coordinator may facilitate the IRB Members' review of less than minimal risk and administrative changes. The IRB Regulatory Coordinator will review all submitted documents and assist in presenting and organizing submissions for IRB Members' deliberation and determination.

The Director of IRB Administration may facilitate IRB Members' review for minimal risk, expedited amendments, expedited renewals, adverse events. The Expedited Reviewer may use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Any protocol revision that entails more than a minimal risk to the subjects must be reviewed by the full IRB at a convened meeting.

Minor changes to informed consent documents that do not affect the rights and welfare of study subjects, or do not involve increased risk or significant changes in study procedures, may be reviewed and approved by the Expedited Reviewer as well. Any protocol or study that has completed all active phases of research and no longer involves risk greater than normal life may be reviewed by an expedited process for renewal. In this case, subjects will be followed in a research setting for long term data collection only. No active research activity or interventions (including low risk activities such as 15ml blood draws) may be occurring.

8. Serious Adverse Event and Safety Reports

A qualified IRB staff person will triage serious adverse event reports (including IND safety reports). The IRB Chairperson and/or PharmD IRB member will review those reports deemed significant. If the Chairperson feels that action is needed to protect the safety of research subjects due to the nature or frequency of reported adverse events, he/she may take such action to the full IRB or designated subcommittee, which will review the adverse events and study in question to determine what action, if any, the IRB should take.

9. Advertisements

The IRB Chairperson or his/her designee may approve new or revised recruitment advertisements or scripts via the expedited process.

10. Translations

Translations of Consent documents by a certified translator may be submitted for IRB approval and will be reviewed in an expedited manner. There are two options available to obtain approval of translated Consent forms;

> Option #1: The IRB-approved consent form is translated by the Sponsor or site and submitted to the IRB. The certification of translation document needs to accompany the form upon submission.

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Option #2: The Investigator (or Sponsor) may submit the IRB-approved English version of the consent to an IRB-approved, UCHealth certified translator for translation.

REFERENCES

21 C.F.R. § 56.110

21 C.F.R. § Part 312

21 C.F.R. § Part 812

45 C.F.R. § 46.101

45 C.F.R. § 46.108

45 C.F.R. § 46.110

Expedited Review Procedures Guidance, OHRP, HHS (2003)
http://www.hhs.gov/ohrp/policy/exprev.html

F. RESEARCH EXEMPT FROM IRB REVIEW

Exempt research is not subject to federal regulations and does not require convened IRB review and approval. Research activities that meet the criteria set forth by the federal regulations that involve minimal risk may qualify for exemption. HHS retains final authority as to whether a particular human subjects research study conducted or supported by HHS is exempt from HHS regulations.

Investigators may not "self-exempt" from review. Exempt research is subject to institutional review as determined by the UCHealth IRB. Although exempt research is not covered by the federal regulations, this research is not exempt from appropriate UCHealth policies on responsible conduct of research or the ethical guidelines of the Belmont Report. Investigators should not "self-exempt" their research for the following reasons:

- No one can be totally objective about their own work.
- Individuals making the exemption determination must have sufficient knowledge and experience to evaluate the risks.

1. Research that Cannot Be Exempt

a. *Research That Involves Greater Than Minimal Risk*

Research eligible for exemption usually involves negligible risks to subjects. When reviewing an application for exempt status, IRB staff apply the "minimal risk" standard. As defined in the federal regulations, minimal risk means that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or

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psychological examinations or tests." Research that involves greater than minimal risk will not qualify for exempt status.

b. *Research Involving Vulnerable Populations:*

Children – 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. In other words, research involving children may not be classified as exempt if the research involves (1) a survey, (2) interview procedures, or (3) observation of public behavior, and the investigator participates in the activities being observed.

Prisoners – Exemptions do NOT apply. Convened full board IRB review is always required.

Other Vulnerable Populations - Persons who are cognitively impaired, economically/ educationally disadvantaged, pregnant, or are fetuses will be reviewed in consideration of their vulnerable status and generally should not be determined eligible for exempt status.

c. *Research Using UCHealth PHI*

Research involving PHI from UCHealth and its associated clinics does not qualify for exempt status. See HIPAA and Human Subjects Research for more information (RI-72).

d. *Research that is subject to FDA Regulations*

Most drug (medication) or device trials involve risk and therefore cannot be exempt. The exceptions are (i) emergency use of a test article for medical care (see Section VII – Research with Test Articles) and (ii) taste and food quality evaluation and consumer acceptance studies (see exempt category 6 in Section IV.2. below).

e. *Research Using UCHealth Employees*

Employees could be subject to coercion, undue pressure or risk of scrutiny. Employees may have concern that volunteering for research may jeopardize their employment status. For these reasons any research processes with employees as subjects involving survey, interview, or other methodology will be required to have UCHealth IRB approval. Often, expedited IRB approval processes are required.

2. Categories of Research that May Be Exempt from IRB Review

Except for the limitations described in Section IV.F.1. above, the following categories are eligible for exemption. Refer to Exempt Categories 2 and 4 (below) for the most commonly used criteria for medical or nursing research.

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Certain categories of research have been designated as exempt from federal regulations related to the use of human subjects. The IRB requires review of all research involving human subjects but imposes different requirements for research meeting the criteria for exemption.

Exempt Category 1:

- Research conducted in established or commonly accepted educational settings, involving normal educational practices, that is not likely to adversely impact (i) students' opportunity to learn required educational content or (ii) 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.

Explanation: Educational research protocols are exempt, providing all of the following conditions are met:

- It is conducted in a commonly accepted education setting.
- "Commonly accepted settings" usually involve public schools, but can include other non-traditional settings.
- It involves normal educational practices. (This criterion most often does not include education in the health system.) It is important for the reviewer to determine whether the procedures change or alter the educational practices for the location. Normal educational practices are activities that would occur regardless of whether the research is conducted.
- It does not increase the level of risk or discomfort attendant to normal, routine educational practices.
- Provisions are made to ensure a non-coercive environment for students who choose not to participate. Research should not be a required part of the curricula. Students should be able to refuse participation. Instructor-researchers should minimize the potential for coercion through the anonymous return of data collection instruments. This can be done by the involvement of a neutral third party, a drop box, and other mechanisms.
- Studies involving surveys or interviews with minors, new curricula or strategies do not qualify for exemption.

Exempt Category 2:

- Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or

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observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, if the IRB conducts a limited IRB review and determines there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Exempt Category 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:

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

  (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

  (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review and determines there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

  - Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions

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would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

- This exemption does not apply if the research involves deceiving the subjects regarding the nature or purposes of the research.

Exempt Category 4:

- Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

  (i) The identifiable private information or identifiable biospecimens are publicly available

  (ii) Information, which may include information about biospecimens is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

  (iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under the Health Insurance and Portability Accountability Act (HIPAA) for the purposes of "health care operations" or "research" (as defined at 45 CFR 164.501) or public health activities and purposes (described in 45 CFR 164.512(b)); or

  (iv) The research is conducted by, or on behalf of a federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002 (44 U.S.C. 3501) , if all the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, and if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501).

Explanation: This exemption only applies to the re-use of data and specimens that were collected for a purpose other than the potentially exempt research purpose. The research materials typically will be publicly available materials, medical records or existing repositories of clinical specimens.

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Data becomes *identifiable* when one or more data elements can be combined with other reasonably available information to identify the person. Identifying information could be linked to specific individuals either directly or indirectly through coding systems.

Investigators may not track subjects to research records through coding because this activity would establish a link. This procedure requires additional IRB approval processes.

Examples of Research Exempt Under Category 4:

- A research study of treatment outcomes for a certain surgical procedure that involves the review of the PI's own patients' charts. The researcher records patient age, sex, diagnosis and treatment outcome in such a way that the information cannot be linked back to the patient.
- A graduate student has access to coded data from a study previously conducted by her advisor and records the information she needs for her research without the code, so that the data being analyzed for the research can in no way be traced back to individual subjects.
- A physician wants to examine slides made from blood collected for therapeutic reasons and considered waste or leftover sampling. Slides are not identifiable, coding keys have been destroyed except for the information about disease and gender of subject they were taken from.

Exempt Category 5:

- Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are 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.

Explanation: In general, research and demonstration projects (e.g., state or city funded public service programs) do not meet these criteria. This category applies to research examining public benefit programs such as Social Security, Medicaid, Unemployment, and Welfare. The project may not involve significant physical invasions or intrusions of privacy and there must be no statutory requirement that an IRB review the project.

This exemption must be specifically invoked only with the authorization of HHS or the Secretary of one of the other federal departments.

Exempt Category 6:

- Taste and food quality evaluation and consumer acceptance studies.

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- 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 FDA or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA).

Explanation: 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. Research that is subject to FDA regulations must be submitted to the IRB for a biomedical review.

Exempt Category 7:

- Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the following determinations:

  (i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained;

  (ii) Broad consent is appropriately documented or there is an appropriate waiver of documentation; and

  (iii) There are adequate provisions to protect subject privacy and maintain the confidentiality of data if there are changes made for research purposes in

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the way the identifiable information or identifiable biospecimens are stored or maintained.

Exempt Category 8:

- Secondary research for which broad consent is required. This exemption permits identifiable private information or identifiable biospecimens to be used for secondary research purposes if the following criteria are met:

  (i) The subject provided broad consent for the secondary research use of identifiable private information or identifiable biospecimens;

  (ii) The IRB conducts a limited IRB review to determine that

  a. there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data, and
  b. the research is within the scope of the broad consent that was obtained from the subject; and

  (iii) the investigator does not include returning individual research results to subjects as part of the study plan.

Note: UCHealth is not implementing Exempt categories 7 and 8 until further guidance regarding broad consent is provided by OHRP.

3. Consent for Exempt Protocols

The Belmont Principle of Respect for Persons generally requires that subjects be given the opportunity to choose whether or not to participate in research. For this reason, voluntary informed consent should be obtained from participants for any exempt research where the investigator will be collecting data through interaction with the participant. The IRB recommends that researchers provide participants with, at a minimum, the information listed below during the consent process and before any data collection begins. In some cases, researchers may find it necessary or appropriate to provide more information.

a. *Minimum Consent Information:*

Consents must include at least the following information:

- The identity/affiliation of the researcher
- A clear description of the study procedures
- A statement that participation in the research is voluntary

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- Contact information for questions about the research

This minimal consent information may take the form of an introductory letter

b. *Changes to or Modifications to Exempt Research*

An exempt determination is not subject to annual continuation/renewal review, as long as the research remains the same. However, all modifications to a project previously deemed exempt must be submitted to IRB for review and certification of exemption prior to implementation. In some circumstances, proposed changes to the protocol may disqualify the project from exempt status, in which case either expedited or full committee review will be required as appropriate.

4. How to Submit an Exempt Application

Investigators must submit a project summary that includes the following information to the IRB department.

- Explanation of the problem to be studied or a copy of the proposal
- Description of the research methods
- Description of the subject population
- Expected duration
- Plan for protecting privacy and confidentiality
- Supporting documents such as data collection tools, surveys, consents, and Invitation to Participate.

5. Exempt IRB Review Process & Criteria

The Exempt Application will be reviewed by the IRB Chairperson or designee. The reviewers 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, all or some of the elements of informed consent may be required by the reviewer.

The IRB will determine that the following criteria are met, where applicable:

- The research presents no more than minimal risk to participants;
- Selection of participants is equitable;
- If the research involves interactions with participants, the circumstances of consent minimize coercion and undue influence;
- Participants will be informed that the study involves research, will be provided with information about the study procedures that the research is voluntary, and will be provided with information about who to contact with questions;

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- Provisions for protecting the privacy interests of participants are adequate; and
- If private identifying data are recorded, provisions for maintaining the confidentiality of data are adequate.

Exempt Application determinations are usually returned within 7-14 days. The IRB will respond in email and writing with the reviewer's determination. The investigator should not begin the research prior to the IRB exemption determination. If an investigator makes an exemption determination themselves, begins the research and then an institutional review determines that the research is not exempt, the conduct of that research prior to the IRB review would be noncompliance and this incident would have to be reported to OHRP. There is a high probability that the data collected prior to IRB review may have to be discarded.

Annual continuing review is not required for exempt research. Investigators may submit a request to close the protocol when research is complete.

Investigators must report modifications that may change the eligibility of the protocol's exempt status. It is the investigator's responsibility to notify the IRB of any changes or modifications that are made to the study's design, procedures, etc., that do not fall within one of the categories of exempt research.

REFERENCES

Colorado Multiple IRB Request for Exemption (March 2015)

Huron Consulting Group; Checklist Exemption Determination On-line

Mayo Clinic IRB Exempt Human Subject Research (May 21, 2014)

Ohio State University Exempt Research (May 2, 2016)

OHRP FAQ's: Exempt Research Determination

21 C.F.R. §§ 56.104 (c) &(d)

21 C.F.R. § 56.110

45 C.F.R. § 46.101 (c)

45 C.F.R. § 46.104

45 C.F.R. § 46.301 (a)

45 C.F.R. § 46.401(b)

G. VULNERABLE POPULATIONS: REVIEWS REQUIRING SPECIAL CONSIDERATION

The IRB shall apply additional protections as necessary to protect potentially vulnerable research participants. When some or all of the participants in a protocol are likely to be

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vulnerable to coercion or undue influence, the IRB should 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, pregnant women, fetuses, neonates, prisoners, adults with impaired decision-making capacity or who lack the ability to consent, students, employees, homeless persons, or persons engaged in illegal activities.

If the IRB 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.

The Common Rule includes specific sections designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs, which are outlined in this section.

1. Pregnancy, Fetuses, Neonates

All research involving pregnant women, fetuses, neonates, the placenta, a dead fetus or any human

fetal tissue (HFT) must be reviewed by the appropriate research committee and the UCHealth IRB. Research involving pregnant women, fetuses, neonates and HFT will have added considerations for review, including increased protections for subjects, restrictions around consent, restrictions on the use of HFT, and addition ethical and privacy considerations.

In particular, the research protocol should be carefully reviewed for any opportunities to improve risk/benefit ratio for both the mother and the fetus. The Investigator's brochure should also be carefully reviewed to determine whether the appropriate animal studies have been completed and the results evaluated. The review should look specifically for fetal loss, deformities, low birth weight, and reduced survival as well as evidence of potential teratogenicity of investigational agents or procedures. Research should not be started in pregnant women unless there is a clear therapeutic need or benefit to the mother or the fetus. In all cases, the risk should be assessed and recorded in the minutes.

a. *Definitions*

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

spontaneous movement of voluntary muscles, nor 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 - a newborn, during the 28 days of life according to the World Health Organization definition. After the first 28 days of life, the baby is considered a child for research purposes.

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Nonviable neonate - a neonate after delivery that, although living, is determined to be 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.

b. *Pregnant Women & Fetuses*

If the UCHealth IRB reviews research that involves pregnant women, fetuses and or neonates, the review process must include one or more individuals who are knowledgeable and experienced in working with these participants. Research involving pregnant women or fetuses may be approved only if **all** of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, (including studies on pregnant animals) and clinical studies, (including studies on non-pregnant women), have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and
    a. The risk to the fetus is caused solely by interventions or procedures that hold out
    the prospect of direct benefit for the woman or the fetus; or,
    b. If there is no such prospect of benefit, (1) the risk to the fetus must be minimal and (2) the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
2. Any risk is the least possible for achieving the objectives of the research; and
3. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
4. Researchers will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;
5. Researchers will have no part in determining the viability of a neonate; and
6. Consent is appropriately obtained. Each individual providing consent must be fully informed regarding the reasonably foreseeable risks and impact of the research on the pregnant woman, fetus, or neonate. If parental consent(s) is obtained before a mother gives birth, but study procedures will not begin until after delivery, the potential subject is a fetus. If parental consent is sought pre-

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natally, the investigator should re-confirm parental permission post-natally before the intervention or study procedures begin.

In the case of research on pregnant women or fetuses, the following consent rules apply:

1. The **Mother** may consent for the study if:
    a. The research holds out the prospect of direct benefit to the pregnant woman, or to the pregnant woman and the fetus, or
    b. If there is no benefit for the woman or the fetus, and both (1) the risk to the fetus is minimal, **and** (2) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
2. The **Mother and the Father** must consent for the study if
    a. The research holds out the prospect of direct benefit solely to the fetus.
    b. 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. Investigators should document the reasons for not obtaining the father's consent in the study records.
3. Minor children who are parents may give permission for their child to participate in research. A minor child who is pregnant may consent to research related to the intended live birth of her child. However, the parent/guardian of the minor parent must give permission for the minor parent to participate in research if it is unrelated to her pregnancy (example: orthopedic injury). Parental permission is not required if the minor parent is emancipated as defined by Colorado State Law. Assent and permission must be obtained in accordance with the protections for research involving children. (See Section VI.G.3.e).

c. *Neonates*

i. Viability

Neonatal research is dependent on viability status of the neonate. Until it has been ascertained whether or not a neonate is viable, a neonate may **not** be involved in research unless the following additional conditions have been met and the UCHealth IRB determines that:

- The research holds out the prospect of enhancing the probability of survival of the neonate
  to the point of viability, and any risk is the least possible for achieving that objective, **or**

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

In addition, the UCHealth IRB must verify that all of the following conditions are met:

- The conditions of legally informed consent of either of the parents of the neonate have been satisfied;
- The appropriate preclinical and clinical studies have been carried out that allow for adequate risk assessment; and
- A neonatologist or pediatrician not associated with the research determined the viability of the neonate.

ii. Viable Neonates

A neonate that is Viable may be included in research only to the extent permitted by and in accordance with the requirements for protections of all human subjects and the protections specific to Children.

iii. Neonates of Uncertain Viability

Neonates of uncertain viability and nonviable neonates may be involved in research if UCHealth IRB determines that:

- The research holds out the prospect of enhancing the probability of survival of the neonate
  to the point of viability, and any risk is the least possible for achieving that objective, **or**
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means, and there will be no added risk to the neonate resulting from the research.

In addition, the UCHealth IRB must verify that all of the following conditions are met:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
- Individuals engaged in the research will have no part in determining the viability of a neonate; and
- The requirements for Neonates of Uncertain Viability or Nonviable Neonates have been met as applicable.

In the case of uncertain viability, the following consent rules apply:

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- Either parent may consent to the participation of the neonate in the research.
- If neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, then the LAR of **either** parent is obtained in accordance with the provisions of permission and consent. Investigators should document the reasons for using the LAR's consent in the study records.
- Each individual providing consent must be fully informed regarding the reasonably foreseeable risks and impact of the research on the neonate.

iv. Nonviable Neonates

After delivery, nonviable neonates may be involved in research **only** when all of the following additional conditions are met:

- Vital functions of the neonate are not artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There are no added risks to the neonate resulting from the research;
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means;
- The legally effective informed consent of **both** parents of the neonate is obtained in accordance with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission **do not** apply. (See Section VI.G.3.e – Consent, Permission & Assent)
- Each individual providing consent must be fully informed regarding the reasonably foreseeable risks and impact of the research on the neonate.

In the case of nonviable neonates, the following consent rules apply:

- The legally effective informed consent of **both** parents of the neonate is obtained in accordance with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission **do not** apply.
- However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of **one** parent of a nonviable neonate will suffice to meet the requirements of this paragraph (with the exception that the consent of the father need not be obtained if the pregnancy resulted from rape or incest). The consent of an LAR of either or both of the parents of a nonviable neonate **will not** suffice to meet the requirements of this paragraph.
- Each individual providing consent must be fully informed regarding the reasonably foreseeable risks and impact of the research on the neonate.

d. *After Delivery: Placenta, Dead Fetus or Fetal Material*

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Research involving the placenta, a dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus, must be submitted to the IRB for review and conducted according to any applicable federal, state, or local laws and regulations regarding such activities. Research protocols involving information or materials that are directly or indirectly identifiable must be submitted to the IRB for review. Living individuals associated with such information or materials are considered research subjects and all relevant protections will apply. If information associated with such material is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are considered research subjects and all relevant protections apply. Research should not be conducted on discarded tissue without prospective informed consent.

e. ***Human Fetal Tissue (HFT)***

Research involving HFT must be conducted in a manner that is respectful to individuals and donors and only in accordance with applicable federal and state laws and regulations. No one who performs abortions may transfer fetal tissue to anyone who conducts research using fetal tissue or transplants fetal tissue for therapeutic purposes in exchange for valuable consideration. Valuable consideration includes money, gifts, barter arrangements, exchange of services, and lease-sharing agreements.

All research involving HFT—or collaborations with external third parties that involves obtaining, procuring, collecting, storing or using HFT—must be reviewed by the appropriate research committee and UCHealth IRB. If information associated with the HFT is recorded for research purposes in a manner that living individuals can be directly or indirectly identified (for example by coding), then those individuals are considered human research subjects and the process will require IRB review.

All research using HFT derived from fetuses considered clinically viable or which otherwise meet the criteria for IRB review, must be submitted to the UCHealth IRB for review and approval. This includes HRT research utilizing external IRBs. Research taking place in multiple regions may require additional reviews by committees such as Research Administration, COMIRB, and CU Anschutz Scientific Ethics Committees. Please refer to the UCHealth Conducting Human Fetal Tissue Research policy for more details.

f. ***Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates***

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates and the research is not approvable under the above provisions, then the IRB will submit the study to the Secretary of HHS who will consult with a panel of experts in pertinent disciplines (for example: science, medicine,

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ethics, law). Based on the recommendation of the panel, the Secretary of HHS may approve the research based on either:

1. The research satisfies the conditions above, as applicable; or
2. The research:
    a. Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
    b. The research will be conducted in accordance with sound ethical principles; and
    c. Informed consent will be obtained in accordance with the provisions for informed consent and other applicable sections of the Code of Federal Regulations Subpart A-D.

References

45 C.F.R. § 46, Subparts B, C, D

45 C.F.R. §§ 46.201,202, 204, 205, 206, 207

C.R.S. § 25-2-111.5

C.R.S. §§ 13-22-103(3), 103.5

UCHealth Policy—Conducting Human Fetal Tissue Research 2.17

COMIRB Policies and Procedures 18.3: Research Involving Pregnant Women, Human Fetuses and Neonates

2. Prisoners

Prisoners constitute an especially vulnerable population that has suffered severe abuses in the past, most notably during war time. In the past, prisoners were viewed as a convenient research population because they are housed in a single location, constitute a large and relatively stable population, and live a routine life. While prisoners should not be deprived of the opportunity to volunteer for research, under prison conditions, prisoners may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Because of this risk for exploitation but the potential that prisoners may wish to participate in research, there are special rules protecting prisoners.

a. *Applicability*

This guidance applies to all research conducted within UCHealth involving prisoners as subjects. Even though the IRB may approve a research protocol involving prisoners as subjects, Investigators are still subject to the Administrative Regulations of the Colorado Department of Corrections and any other applicable state or local law. If research will

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involve the Bureau of Prisons or other federal agencies under the Department of Justice, then Investigators will also be subject to the Department of Justice regulations for human research protection.

Research involving Prisoners of War is not permitted for research sponsored by the Department of Defense (DOD) Addendum. The IRB must be aware of the definition of "prisoner of war" by the DOD component granting the Addendum. Research involving any person captured, detained, held or otherwise under the control of the DOD personnel (military and civilian, or contractor employee) is prohibited.

b. *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 that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. Common examples include:

1. Individuals detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing.
2. Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to criminal prosecution or incarceration.
3. Parolees who are detained in a treatment center as a condition of parole.

An individual who is free to move about does not meet the definition of "prisoner." A person under house arrest who cannot leave the premises is considered a prisoner. One that can leave would not be.

Prisoner Representative – Someone who can represent the concerns that prisoners might have based on his or her knowledge of prison conditions and the life of a prisoner. Suitable candidates include former prisoners, prison chaplains, or social workers dealing with prisoners and/or their families. Prisoner advocates may also qualify as a Prisoner Representative.

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. (Note that this definition of minimal risk differs from the definition used outside of the context of prisoner research.)

Engagement – OHRP guidance suggests that "engagement in research" involving prisoners can include: (a) seeking the informed consent of prisoners to be subjects; (b) using, studying or analyzing identifiable private information, or identifiable specimens, obtained from prisoners; and (c) surveying prisoners for a research study.

c. *IRB Procedures and Responsibilities*

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1. The IRB should ensure special protections are incorporated into human subject research that are adequate and minimize the potential for risk or harm.
2. All research reviewed involving prisoners, including data about prisoners, will be reviewed at a fully convened meeting. Initial applications, amendments, and continuing review that includes prisoner research are reviewed by the fully convened board. At least one member of the IRB must be a prisoner or a Prisoner Representative with appropriate background and experience to serve in that capacity and must be present at the IRB meeting when reviewing research involving prisoners.
3. A majority of the IRB (exclusive of prisoner members or representatives) shall have no association with the prison(s) involved, apart from their membership on the IRB.
4. The Prisoner Representative must be a voting member of the IRB (he or she may be listed as an alternate and become a voting member when needed).
5. The Prisoner Representative must receive all review materials pertaining to the research (same as primary reviewer).
6. The Prisoner Representative must be present at a convened meeting when the research involving prisoners is reviewed. If the Prisoner Representative is not present, research involving prisoners may not be reviewed or approved. The Prisoner Representative may attend the meeting by phone, video-conference, or webinar, as long as he/she is able to participate in the meeting as if he/she were present in person at the meeting.
7. The Prisoner Representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.
8. Prisoners cannot be involved in planned emergency research where informed consent has been waived.
9. The IRB must make and adequately document the required determinations discussed in Section VI.G.2.d below.

d. ***Approval Criteria***

In addition to the approval criteria applicable to all human subjects research, the IRB must make and adequately document the following findings before approving research involving prisoners:

1. The research under review falls into one of the following permissible categories of research:

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d. 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 subjects;

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

f. Research on conditions particularly affecting prisoners as a class (e.g. research on social and psychological problems such as addiction or sexual assault);

g. Research on practices that have the intent and reasonable probability of improving the health or well-being of the subject. (If the study involves allocation of prisoners to a control group that 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 note to approve in the Federal Register.)

2. Any possible advantages or compensation 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 opportunities for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
5. Information is presented in language understandable to the subject population.
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decision regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
7. Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examinations or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

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e. ***HHS/OHRP Certification***

After the IRB reviews prisoner research that is supported by the HHS, the IRB must notify OHRP that it has fulfilled the requirements related to protection of prisoners and provide the following:

f. ***The name and qualifications of the IRB Prison Representative;***

g. ***A reasonably detailed description and documentation of the research (e.g. a copy of the protocol, IRB application forms, the institution's FWA number, the reviewing IRB's registration number, date of IRB review);***

h. ***The category of permitted research; and***

i. ***Documentation of the additional required findings.***

In a multicenter study, each institution must provide this certification "unless (a) an institution relied upon the review of an IRB operated by another institution engaged in the research; and (b) that IRB or the other institution certified to OHRP on behalf of both institutions.

Research involving prisoners may not proceed until OHRP has reviewed the IRB's determination and concurs. This requirement must be detailed in the IRB meeting minutes and a feedback letter to the Investigator. A letter informing the Investigator that the IRB has received concurrence from OHRP will be sent by the IRB. Only after receiving the letter may the Investigator begin the study.

j. ***Waiver for Epidemiology Research***

In certain circumstances, the Secretary of HHS has waived the requirements that: (1) research fall into a permissible category or (2) that the advantages of participation in research must not be of a magnitude that would impair the prisoner's ability to weigh the risks of the research against the benefits. Research that is conducted or supported by HHS and involves epidemiologic studies that do not fit the previously outlined categories, and meet the following criteria are eligible for such waiver: (68 FR 36929, June 20, 2003):

The sole purpose of the research is:

- To describe the prevalence or incidence of a disease by identifying all cases, or
- To study potential risk factor associations for a disease, and
- Where the IRB has approved the research and fulfilled its duties under 45 C.F.R. § 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

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- 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 permissible research categories set out in 45 C.F.R. § 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.

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.

k. *When a Subject Becomes a Prisoner During the Study*

When a participant in a research study becomes a prisoner—and the study has not been approved with the additional protections for prisoners—the Investigator must report the situation to the IRB immediately. If a subject is incarcerated temporarily while enrolled in a study and the temporary incarceration has no effect on the study, then the subject may remain enrolled in the study. If the incarceration has an effect on the study, then the IRB will review the involvement of the subject as a prisoner.

If a subject becomes a prisoner during the study, the Investigator must immediately suspend research on that subject. This includes suspension of all interactions, interventions, and obtaining PHI for research purposes. The IRB must then re-review the study pursuant to the requirements for protection of prisoners (under Subpart C of the regulations). If the IRB approves the research, the Investigator must also receive OHRP authorization as required. Unless the IRB reapproves the research for inclusion of prisoners and OHRP concurs, the newly incarcerated individual must be withdrawn from the study.

In special circumstances in which the Investigator asserts that it is in the best interests of the subject to remain in the study while incarcerated, the IRB may determine that the subject may continue to participate in the research until the Subpart C requirements are satisfied. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, the IRB may determine that the subject may continue to participate in the research and inform OHRP of the IRB's decision along with the justification.

l. *Local Review*

In the case of multisite studies, there is a need for advocates representing prisoners across all study sites. Sufficient knowledge of prisons at each site is necessary to help

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insure that the IRBs will be cognizant of potential risks and benefits of research conducted at all participating penal institutions. This speaks to the need for local IRB review in most cases, in order to make knowledge decisions regarding the ethics of specific protocols in specific locales. (Bankert page 380)

m. ***Research of Prisoners Who are Minors***

When a research subject is both a prisoner and a minor, in addition to Subpart C above, the IRB must also consider Subpart D referenced below in Section VI.F.3. The OHRP has provided specific guidance on this issue, suggesting that an adolescent detained in a juvenile detention facility would be considered a prisoner, and Subpart D would likely apply. If the minor is tried, convicted, and sentenced as an adult, then depending on state law, the prisoner may be constructively emancipated and can legally consent to participate in research. IRBs that choose to recognize constructive emancipation of an incarcerated minor should do so only after careful review of all considerations including vulnerability of the minor, developmental age, and the fact that the rights of the minor's parents to direct the child's activities have been involuntarily subjugated to the state department of corrections.

n. ***Additional Considerations***

Due to the income disparity, compensating prisoners the same amount that would be paid to non-prisoners participating in the research may be coercive. On the other hand, paying prisoners less that non-prisoners may be exploitative. The suggested approach is to pay prisoners a rate comparable to compensation for other prisoner tasks. The remaining balance would go to the prisoner's family (or perhaps to the prisoner when the prisoner is released) or to a general educational or recreational fund under the control of prison inmates.

References

45 C.F.R. Part 46, Subpart C; 21 C.F.R. Part 50, Subpart C

Wisconsin Department of Workforce Development Child Support Bulletin (Sept. 27, 2005)

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Involvement of Prisoners in Research (March 23, 2003)
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D. Vulcano, "Research Involving Prisoners in Non-Prison Settings: FDA and OHRP Regulations"

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"Waiver of the Applicability of Certain Provisions of Department of Health and Human Services Regulations for Protection of Human Research Subjects for Department of Health and Human Services Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects," 68 Fed. Reg. 36929-31 (June 20, 2003)

3. Children

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children.

a. *Definitions*

- Assent - A child's affirmative agreement to participate in research. Mere failure to object, absent affirmative agreement, should not be construed as assent.
- Child - A person who has not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted. In Colorado, the age of competence is 18 years old.
- Emancipated Minor – A person who has not yet attained the age of legal competency, but who is entitled under state law to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation. In Colorado, an emancipated minor is at least 15 years old who is living separate and apart from his or her parents or guardian and is managing his or her own financial affairs, or any minor who has contracted a legal marriage.
- 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.
- Mature Minor - Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (example: consenting to certain types of medical care). Note that a mature minor is not necessarily an emancipated minor.
- Permission - The agreement of parent(s) or legal guardian to the participation of their child or ward in research or clinical investigation

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- Parent – A child's biological or adoptive parent
- Ward – A child who is placed in the legal custody of the state or other agency, institution, or entity, consistent with applicable Federal, State or local law.

b. *IRB Consultation When Reviewing Research Involving Children*

An IRB considering a protocol involving children as participants is required to:

- Assess its needs for pediatric expertise among the IRB voting membership to assure that it possesses the professional competence necessary to review the specific research activities; and
- Consider inclusion of one or more individuals who are knowledgeable about and experienced in working with children. To fulfill this requirement, the IRB may invite nonvoting individuals to assist in the review of issues which require expertise beyond, or in addition to, that available among voting IRB members.

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

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

In assessing the possible *benefits* of research intervention, the IRB should consider the variability in health status among potential subjects. A potential subject might be a normal, healthy child, or a child who has been exposed to a disease or a toxin. A child may be in an early state of disease, or may be suffering from disease or other significant medical condition. The IRB must take into account the current health status of a child and the likelihood of progression to a worsened state without research intervention.

d. *Allowable Risk Categories*

The federal regulations require IRBs to classify research involving children into one of four risk categories and to document their discussions of the risks and benefits of the research study. Each of the risk categories will require a different level of consent and assent, which are discussed in further detail below. The four risk categories for research involving children that may be approved by IRBs are as follows:

i. Minimal Risk
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

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tests (i.e., minimal risk). In this case, the IRB may find the permission of one parent sufficient.

ii. Greater Than Minimal Risk with Direct Benefit
Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject, including the following findings:

- The risk is justified by the anticipated benefit to the subjects;
- The relationship of risk to benefit is at least as favorable as any available alternative approach.

In this case, the IRB may find that the permission of one parent is sufficient, but the assent of the child is required. Note that protocols with placebo arms are not considered to have direct benefit and require two parent signatures.

iii. Greater than Minimal Risk, No Benefit, Generalizable Knowledge
Research involving greater than minimal risk with no reasonable prospect of direct benefits to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. The IRB must make the following findings:

- 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;
- The intervention or procedure is likely to yield generalizable knowledge that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

For research in this category, permission of 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. The child must assent to the research.

Research involving a placebo arm may fall into this category. Each study arm requires a separate pediatric assessment. If approved, permission of both parents, and the child's assent, is required for placebo arm research.

iv. Does Not Qualify For Risk/Benefit
Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.

- All research in this category must be approved by the Secretary of HHS, and a panel of experts.

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If approved by HHS, a panel of experts, and the IRB, the consent of either both parents, or legal guardian is required, and the assent of the child is required.

e. *Consent, Permission & Assent*

The IRB 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;
- when only one parent has legal responsibility for the care and custody of the child;
- the research falls into a minimal risk category and the IRB has determined that the permission of one parent is sufficient; or
- state law permits the minor to consent to treatment.

Parents or guardians must be provided with the basic elements of consent required for all studies, as well as any additional elements the IRB deems necessary. (See Section VIII – Informed Consent). When the IRB finds that the permission of one parent is sufficient for research to be conducted, the IRB's determination must be documented in the meeting minutes.

i. Process of Assent from Children

When the child's assent is required, Because "assent" means a child's affirmative agreement to participate in research, 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. The IRB has the discretion to judge children's capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

When reviewing the proposed research activity and the form and content of information presented to subjects, and when judging whether children are capable of assent, the IRB must consider the age, maturity, and psychological state of the children involved. 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. For example:

- For research activities involving children whose capacity to understand resembles that of adults, the assent procedure should 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

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example, what the experience will be, how long it will take, whether it might involve any pain or discomfort).

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 through 11 years of age. Written assent using a written document for the children to sign may be sought for older children. The following guidelines apply for children of different ages:

- Age 6-7: A simple oral description of the child's involvement is given to the subject and oral assent is requested. The procedure may be documented on the informed consent form by the presence of the signature of a witness.
- Age 8-13: A more complete oral description of the research (in layman's terminology) is given to the subject. Verbal assent is requested. The procedure may be documented on the informed consent form by the signature of a witness.
- Over Age 13: Written assent should be requested from both parent and child, using age-appropriate and background appropriate documents.

Occasionally, the parents and the child may not agree. 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. There may be 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 IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent below.

ii. The Assent Form

Researchers should draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

- Explain why the research is being conducted;
- Describe what will happen and for how long or how often;
- State that it is up to the child to participate and that it is okay to say no;

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- Explain if it will hurt, and if so, for how long and how often;
- Explain the child's other choices;
- Describe any good things that might happen;
- State 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.

iii. Consent by Minors

As a general rule, minors—those under the age of 18—a child's parents or guardian must consent to the child's medical care or the child's participation in research. Under Colorado law, a minor may consent to medical treatment in certain circumstances. The UCHealth IRB has interpreted Colorado law to permit minors to consent to research procedures that is directly related to the clinical treatment for which minors may legally consent. For research conducted in states other than Colorado, the research and consent must comply with that state's laws.

In the absence of an emergency, only the parents or legal guardian of a patient under the age of 18 years can give a valid consent on behalf of the minor with the following exceptions:

1. If a minor is at least 15 years of age and is an Emancipated Minor, he or she may give valid consent to treatment;
2. A minor parent, may request and consent to nursing, medical, dental and surgical care for his/her own child, even though the minor parent cannot consent for his/her own care.
3. A pregnant minor may approve the prenatal, delivery, and post-delivery medical care related to the intended live birth of a child.
4. Minors can consent to their own treatment, regardless of age or marital status for the following treatments and procedures:
    - medical care and treatment for use of addiction to drugs
    - alcoholism or intoxication or incapacity due to alcohol
    - venereal disease
    - AIDS or HIV testing (If the minor is less than 16 years or not emancipated the minor parents or legal guardian may be informed by the facility or physician of the consultation, examination and treatment. The physician or other health

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care provider shall counsel the minor on the importance of bringing his/her parents or guardian into the consultation, examination or treatment

- birth control or family planning
- sexual assault (prior to an examination or treatment, the physician must make reasonable efforts to notify the parent or legal guardian)
- an un-emancipated minor of 15 years of age or older may seek mental health services

Certain procedures may not be consented to by minors under the age of 18:

- organ transplant,
- donation of blood,
- permanent sterilization,
- execution of a living will for termination of life support and electroconvulsive treatment (which may be per formed on a minor 16 years of age or older, but only with the approval of two psychiatrists and a parent or guardian).

Justification must be provided as to why the inclusion of this population is necessary, how the research questions focuses on an issue unique to subjects in this population, and that the research does not extend beyond the provision of treatment as outlined in the state statute.

iv. 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, 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. [45 CFR 46.409]

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 IRB) with the research, the investigator(s), or the guardian organization.

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v. Waiver

The IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

- The research meets the generally applicable provisions for waiver (See Section VIII.C) and the IRB 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).
- 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.

f. *Exemption from Review*

The exemption at 45 CFR 46.104(d)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children covered by Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed. The remaining exemptions in apply to research involving children.

References

45 C.F.R. Part 46 Subpart D; 21 C.F.R. Part 50 Subpart D

C.R.S. §§ 13-22-101 through 106.

C.R.S. §§ 25-4-402 through 405.

Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products, 78 Fed. Reg. 12937-12951 (Feb. 26, 2013)

FDA Final Rule: Additional Safeguards for Children in Clinical Investigations of FDA Related Products, effective March 28, 2013

IRB Guidebook: Chapter IV Special Classes of Subjects, Children and Minors - OHRP

UCHealth Policy Consent to Treatment

University of Colorado at Denver; Children's Hospital; University Hospital Human Subject Research Committee

UCLA OPRR HRPP Special Subject Populations

COMIRB Policy 18.2 - Research Involving Children

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4. Decisionally Challenged or Unable to Provide Consent

Research involving subjects who are mentally ill or subjects with impaired decision making capacity warrant special protection. Some participants with conditions leading to diminished functional abilities might be less likely to understand the purpose or voluntary nature of research, or to anticipate reasons against their participation than participants with unimpaired functional abilities. For this reason, it may be ethically appropriate to limit risk to impaired participants and include additional protection.

Although there are no federal regulations that require specific additional protections to address the needs of this vulnerable group, the IRB will generally follow the recommendations governing the conduct of research in children and of specific recommendations made by the National Bioethics Advisory Commission.

a. *Definitions*

Decisionally Challenged – includes adult subjects with diminished decision making capacity who are:

- incompetent to consent,
- cognitively impaired, or
- have altered decisional capacity due to environment or situation.

Incompetence – when an individual is unable to manage his or her own affairs; often used interchangeably with incapacity

Cognitively Impaired – having a psychiatric disorder (e.g. psychosis, neurosis, personality or behavioral disorder) an organic impairment (e.g. dementia) or a developmental disorder 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 drugs or alcohol, suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severe physical handicaps may also have a compromised ability to make decisions in their best interests.

Altered Decisional Capacity – an individual who generally has the ability to provide informed consent or refusal, but this ability is compromised by external factors, such as time limitations, medications, physical pain, or stress. To give informed consent, a subject must be given all relevant information pertinent to the decision and able to recognize that a decision is needed and process the information (i.e. discuss it, remember it, evaluate various factors and understand the consequences). If this process is compromised, the potential subject may be considered to have Altered Decisional Capacity.

b. *IRB Review & Approval*

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i. IRB Composition
The IRB membership must include at least one member who is knowledgeable and experienced working with decisionally challenged subjects. Consideration may be given to adding another member who is a family member of such a person or a representative of an advocacy group for that population.

ii. Approval Criteria
Research involving subjects with impaired decision making capacity may only be approved when all of the following conditions apply:

- Only incompetent persons with impaired decision making capability are suitable research subjects; competent persons are not suitable research subjects. The Investigator must demonstrate a compelling reason to include such individuals as subjects.
- The proposed research contains no significant risks, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. If the research presents more than a minimal risk with no prospect of direct benefit, but is of vital importance to the vulnerable population, the risk presented must be no more than a minor increase over minimal risk.
- Procedures have been devised to ensure that the participant's representatives are well-informed regarding their roles and obligations to protect incompetent subjects. LARs/MDPOAs must be given descriptions of both proposed research studies and the obligations of the subject's representatives, including the obligation 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 subject's best interests.

c. *Additional Safeguards*

Individuals with diminished capacity to consent have the right to be involved in research related to their illness or condition. Federal regulations require additional safeguards to protect the rights and welfare of subjects that are "likely to be vulnerable to coercion or undue influence." Because individuals with diminished capacity are vulnerable, the IRB should institute additional safeguards to protect these individuals.

For example, subjects should be recruited from among non-institutionalized populations whenever possible. In institutional settings, issues of independence and coercion may be factors that may compromise the voluntary nature of their participation in research and should be given extra consideration.

Additionally, when seeking consent of adults with diminished decision making capacity, the IRB should consider requiring the subjects' assent, as you would when children are subjects of research. Additional protections for adults with diminished decision making capacity should be proportional to the severity of the decisional impairment and/or level of risk.

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Investigators and the IRB should consider additional safeguards, balancing the need for protection with the individuals' right to autonomy. Examples of additional safeguards include (but are not limited to) the following:

- Securing an independent assessment of the participant's capacity to consent.
- Identification of an LAR or a medical durable power of attorney (MDPOA) who has the authority to consent to the adult's participation in research.
- Obtaining assent from the participant, in addition to surrogate consent.
- Regular assessment of the participant's capacity and provisions for re-consenting a participant who regains capacity during the course of research.
- Involvement of family members familiar with the participant's personal values.
- Designation of an individual at the beginning of the study to serve as a LAR or MDPOA for use if the participant's decision making capacity becomes compromised during the study.
- Use of informational/educational techniques to enhance communication and understanding during the consent/assent processes.
- Including "waiting periods" in the consent/assent processes.
- Involvement of a research subject advocate.
- Limiting the risks to which an adult unable to provide informed consent is exposed when direct benefits are not anticipated.
- Use of an independent monitor or data monitoring committee.
- Observation of the informed consent/assent processes by a third party as designated by the IRB.

d. ***Assessing Capacity***

Prospective adult participants with impairments to functional abilities are presumed to be capable of providing consent to enroll and participate in a research study unless there is substantial evidence that they are not capable. Researchers and IRB members should not consider the mere presence of a condition that leads to diminished functional abilities as indicative of a lack of capacity to consent.

Investigators and the IRB should consider the capacity of potential research participants to provide informed consent and include methods to assess capacity appropriate to the research. Key factors in individuals' consideration of research participation include an appreciation of how the risks, benefits, and alternatives to participation apply to them personally. When the research involves greater than minimal risk, an independent assessment of the potential participant's capacity to consent should be performed (or confirmed), except in unusual circumstances where the IRB determines that the research

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is of critical importance and could not be conducted if the independent assessment were to be required. Methods to provide independent assessments include subjective assessments made by a qualified professional independent of the research team or use of a valid objective instrument(s) designed to evaluate capacity. Cognitive tests and competence assessment instruments alone cannot provide the basis of the evaluator's determination regarding a participant's capacity to consent, and should at most supplement or support the evaluator's expert judgment.

For studies involving adult participants likely to experience fluctuating functional abilities, IRB members should consider whether:

- The consent process plans to avoid, if feasible, periods during which prospective participants are likely to experience greater than normal impairment to functional abilities (e.g. medication schedules, acute intoxication, or episodic increases symptoms);
- Procedures are described for obtaining the consent of any participant who is initially judged incapable of providing consent, but regains the capacity to consent;
- An adult with temporary diminished decision making capacity or other adult unable to provide informed consent may participate in research only if a LAR, MDPOA or proxy for that adult can give consent for participation in the research. If the participant regains (or develops) the capacity to consent, then his/her informed consent must be obtained for any further research.

e. *Consent, Proxy Decision-Makers & Assent*

All adults should be presumed capable of providing informed consent unless there is specific evidence that an individual's condition/disability would impair reasoning or judgment, or other indication that the individual is unable to understand and choose whether or not to participate in research.

In Colorado, for therapeutic research, the designation of a proxy decision-maker or MDPOA for the consent process may be obtained with prior approval from IRB. The proxy decision making plan should be submitted to the IRB for approval when conditions of temporary impairment are anticipated.

When no LAR is available, the attending physician, or his/her designee, will make reasonable efforts to locate as many interested persons as practicable (such as: spouse, parents, adult child, adult sibling, adult grandchild, close friend). The treating physician will meet with the interested persons and (a) will inform them of the patient's lack of capacity; (b) will advise them that a proxy should be selected; (c) will advise them of the availability of assistance of the medical ethics committee; and (d) will note in the medical record the parties present and their relationship with the patient. All interested persons will make reasonable efforts to reach a consensus as to one decision maker (this should be

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someone who has a close relationship with the patient and is most likely to be currently informed of the patient's wishes).

f. *Assent & Objection*

An adult unable to provide informed consent to participate in research may be able to assent to participation. The IRB is responsible for determining when the assent of some or all such adults is required in proposed research and the appropriate method for documenting the adult's assent (if any), as described below.

Assent processes are to include the key elements of informed consent and are to be provided in language appropriate for an adult with diminished decision making capacity, based on the nature of the study and the expected ability of the prospective participant(s) to understand the purpose and the procedures involved in the research. (See Section VIII - Informed Consent)

If a cognitively impaired adult subject objects to participate in a research study, that decision should be binding, except when the individual's participation is specifically authorized by a court of law, the intervention is expected to provide a direct health benefit to the subject, and the intervention is available only in the context of the research. This is in keeping with the Belmont Report recommendation that "despite the fact that consent may be obtained from an LAR or guardian, the feelings and expressed wishes of an incompetent person should still be respected." The lack of objection should not be interpreted as assent.

g. *Legal Counsel*

The IRB will seek legal counsel to assess state laws that might affect the participation of legally incompetent persons and/or the role of guardians in the consenting process as required.

References

45 C.F.R. § 46.111

C.R.S. § 15-18.5-103

Proxy Decision Maker for Medical Treatment and Medical Durable Power of Attorney Policy

Assessing Capacity Policy

UCHealth Policy: Proxy Decision Maker for Medical Treatment

UCHealth Policy: Advanced Directives

S.Y.H. Kim, Evaluation of Capacity to Consent to Treatment and Research, Ch. 8, 151-171, Oxford Univ Press (2010)

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National Bioethics Advisory Commission Report and Recommendations on Research Involving Persons with Mental Disorders That May Affect Decision Making Capacity1998

UBACC – A New Brief Instrument for Assessing Decisional Capacity for Clinical Research Dilip V Jeste, MD et al (UCSD) Archives General Psychiatry Vol. 64 (No. 8), August 2007

The Ohio State University Human Research Protection Program Policies and Procedures

AAHRPP Tip Sheet 26 Reviewing Research Involving Adult Participants with Diminished Functional Abilities Related to Capacity to Consent

H. STUDY COMPLETION

The completion or termination of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows closure of the files, as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

1. Definitions

Accrual Closure or Closed to Accrual – Means that no additional subjects will be enrolled in the study. Study activity is ongoing and may include intervention or interaction with subjects, continued use of a drug or device, and/or data analysis. This action is either permanent or temporary.

Permanent Study Closure – A study is closed when accrual of research participants is complete and all research activities have ceased. This means no interaction/intervention is planned for the purpose of research with research participants and no long-term follow-up. Data collection and analysis are complete.

Site Closure – The PI has decided to withdrawal UCHealth from the study, the study may or may not still be open to accrual at other sites.

Suspension - An action taken by the IRB or other body with such authority. It is a temporary or permanent halt to some or all research procedures short of a termination until the IRB determines whether the research may recommence (with or without modifications to the research) or whether the research must be terminated.

Temporary Closure – A study may be temporarily closed or closed to enrollment when there is a pause in the conduct of research or recruitment. This often happens when conducting an interim analysis.

Termination – The clinical study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated. The IRB may also terminate a study for cause, therefore halting further research.

2. Determining When a Project May Be Closed

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HHS-supported protocols maybe closed when individually identifiable follow-up data are no longer being collected on subjects enrolled in an HHS-supported protocol and analysis that could indicate new information is complete.

Multi-site industry studies may be closed when the Investigator submits his or her final report. Sponsors often wait to permanently close studies until all sites have completed all of their activity. Accrual or "arm" closure is not considered to be the study completion. A study will not be closed until all data is collected and analyzed.

VII. RESEARCH WITH TEST ARTICLES

A. PLANNED RESEARCH IN EMERGENCY SETTING

The IRB may approve an exception to the requirements for informed consent for research about life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent from research participants or their LARs. The purpose of this policy is to outline the additional protections required by the regulations for planned emergency research where the requirements for informed consent are waived. Because of the regulatory limitations relating to research involving prisoners, fetuses, pregnant women, and human in vitro fertilization, a waiver of informed consent cannot be approved for emergency research involving these populations.

1. Definitions

Community Consultation - A process of consulting with the community via open public forums. These forums will provide the opportunity for discussions, and encourage the solicitation of opinions from the community in which the study will take place. If several communities are sites or if the researchers are not in the same community as the subject, then both communities should be consulted.

Family Member - For purposes of the waiver of informed consent for emergency research, any one of the following legally competent persons: spouse, parent, child (including an adopted child), brother, sister, spouse of a brother or sister, and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Life Threatening - Disease or conditions where the likelihood of death is high unless the course of the disease/condition is interrupted. The condition need not be immediately life threatening or result in death. The subjects must be in a life-threatening situation requiring intervention before consent from a LAR is feasible. For example, people with conditions like coma, stroke, and head injury whose likelihood of survival is not known within the therapeutic window of treatment. The informed consent waiver provision is NOT intended for non-emergent coma where patients have already been in a comatose state for a long period of time.

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Planned Emergency Research - Research involving human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who because of their condition (e.g., traumatic brain injury) cannot provide informed consent.

Prospect for Direct Benefit - The information from animal and preclinical studies, other clinical data (e.g., use of the product in another setting or for another diagnosis or in a different study population) or other evidence should support the potential for the investigational product to provide a direct benefit to the individual subjects.

Public Disclosure - Dissemination of information (i.e., one-way communication) to the community(ies), the public, and researchers about the emergency research. This may take the form of newspaper, radio spots, and news reports.

Therapeutic Window - The time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect (diagnostic or therapeutic).

2. General Information

Persons with life-threatening conditions who cannot provide informed consent or refuse research participation are considered to be a vulnerable population. The lack of subject autonomy and inability of subjects to provide informed consent require that additional protections are provided in the review, approval, and performance of this research.

Prospective and continuing IRB reviews are required for planned emergency research. The IRB must approve both the research and the exception to the requirements for informed consent (i.e., waiver) by finding and documenting that the regulatory criteria described below are met. The requirements for planned emergency research are subject to FDA regulations, and differ slightly from the requirements for research subject accordingly to HHS regulations. All planned emergency research at UCHealth must meet the requirements described below in “Exception to the Requirements for Informed Consent”.

3. Approval Criteria

The IRB may approve emergency research **without** requiring informed consent be obtained from subjects or their LARs only if the IRB finds and documents that each of the eight (8) requirements outlined in this section have been met. A licensed physician who is a member (or consultant) of the IRB and who is not otherwise participating in the research must agree with the IRB’s determination that the criteria for consent waiver are met. Documentation of the physician’s concurrence is also required for approval. The IRB meeting minutes should specifically record the physician’s vote when planned emergency research is reviewed.

The approval criteria for the exception are:

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1. The human subjects are in a life-threatening situation. Intervention is required before consent from an LAR is feasible.
2. Available treatments are unproven or unsatisfactory, based on the fact that relative risks and benefits of the proposed intervention are unknown or thought to be equivalent (or better) compared to standard therapy.
3. The collection of valid scientific evidence is necessary to determine the safety and efficacy of the intervention.
4. Obtaining informed consent is not feasible because of *all* of the following:
    - The subjects will not be able to give their informed consent as a result of their medical condition(s);
    - The intervention under investigation must be administered before consent from the subjects' LAR, MDPOA or proxy is feasible; and
    - There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the research.
5. The research could not practicably be carried out without the IRB approval of a waiver of informed consent.
    - For example, recruitment of subjects providing informed consent could bias the science, the science is less rigorous as a result of restricting the research to subjects who can provide consent, or the research would be unreasonably delayed by restricting it to consenting subjects
6. Participation in the research holds out the prospect of direct benefit to the subjects because appropriate animal and other preclinical studies have been conducted and the information delivered from those studies (and related evidence) supports the potential for the intervention to provide a direct benefit to individual subjects.
7. Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, and what is known about the risks and benefits of the proposed intervention or activity.
8. The protocol defines the length of the potential therapeutic window based on scientific evidence.
    - The investigator has committed to attempting to contact a LAR for each subject within that window of time and, if feasible, to asking the LAR, MDPOA or proxy for consent rather than proceeding without consent.
    - Investigators will summarize efforts made to contact LAR and provide this information to the IRB at intervals requested by the IRB.

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4. Additional Protections for Patient Safety

Additional notifications of the community regarding the rights and welfare of subjects, include at least:

- The IRB should consult with the community and consider community input when reviewing the research. The IRB should consult with representatives of the geographic communities in which the research will be conducted and from the disease related subjects or people affected by the condition will be drawn (e.g. young males in trauma research).
    - Examples: Holding a public meeting in the region, conducting a telephone poll, establishing a separate panel of community members to consult on the project, and adding unaffiliated members to the IRB who are representative of the community
- Prior to initiation of the research, the plans for research should be disclosed publically, including the risks and expected benefits to the communities and subjects affected by the research. This may include newspaper articles, press release, and posters.
- Following completion of the research, sufficient information should be disclosed publically to apprise the community and researchers of the study, including the demographic characteristics of the research population and its results.
- An independent data monitoring committee should be established to exercise oversight of the research. FDA interprets this regulatory provision to permit a sponsor to either establish an independent committee or to secure the services of an already established committee to exercise oversight of the clinical investigation.

5. Informed Consent

The IRB must review and approve an informed consent process and consent document. The approved informed consent procedures and consent document are to be used with subjects, their LARs, or their family as soon as possible.

If obtaining informed consent is not feasible (and a LAR is not reasonably available), the investigator will attempt to contact within the therapeutic window the subject's family member who is not a LAR, and asking whether he/she objects to the subject's participation in the research. The following guidelines apply:

- Only one family member must be consulted and agree (or object) to the subject's participation in the research.
- If more than one family member is present and family members disagree, the family members must work out the disagreement to before the subject may be enrolled.

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- Investigators will summarize efforts made to contact family members and provide this information to the IRB at the time of continuing review.
- The IRB will approve procedures to inform the subject, the subject's LAR (if the subject remains incapacitated), or a family member (if the LAR is not reasonably available) of the following at the earliest feasible opportunity:
    - The subject was included in the study;
    - Details of the research and other information contained in the informed consent document; and
    - The subject's participation may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- If a LAR or family member is told about the study and provides consent and the subject's condition subsequently improves, the subject must be informed as soon as feasible. If the subject no longer wishes to participate, they may withdraw their participation.

If a subject is enrolled in the study with waived consent and the subject dies before a LAR or family member can be contacted, information about the study is to be provided to the subject's LAR or family member, if feasible.

6. Research Subject to FDA Regulations

The IRB must confirm and document that a separate investigational new drug (IND) or investigational device exemption (IDE) is obtained for use of the investigational drug, biologic, or device to be studied in the research that clearly identifies the protocol as one that may include subjects who are unable to consent. A separate IND/IDE is required even if an IND for the same drug or an IDE for the same device as the one to be studied already exists.

If the IRB cannot approve the research either because of relevant ethical concerns or the criteria described above are not met, documentation of the IRB's findings will be provided in writing to the investigator and sponsor within 14 days. The Sponsor must promptly disclose this information to FDA and to investigators who have been asked to participate in the research or a "substantially equivalent clinical investigation" and to other IRBs that have been or are asked to review this or a substantially equivalent investigation by that sponsor.

7. Investigator Responsibilities

The IRB research project application must describe additional protections of the rights and welfare of the subjects including at least:

- Explanation of any opt out mechanisms for potential participants

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- A plan for public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

The proposed investigational plan must define the length of the potential therapeutic window based on scientific evidence. The investigator must commit to attempting to contact an LAR for each subject within that window of time and, if feasible, to asking the LAR contacted for consent within that window rather than proceeding without consent.

- If obtaining informed consent is not feasible within the therapeutic window and a LAR is not reasonably available, the investigator must contact, if feasible, the subject's family member and ask whether he or she objects to the subject's participation in the clinical investigation.
- The Investigator must summarize efforts made to contact LAR and/or family members and makes this information available to the IRB at the time of continuing review.
- A plan for training should be included in the application.

Prior to beginning the study, the investigator should ensure that all individuals, including first responders, who will carry out study-related tasks, are informed of their training program obligations and associated regulatory requirements for conducting the research.

8. IRB Responsibilities

In addition to the responsibilities listed previously, the IRB must find and document that the public disclosure will have or has taken place prior to the initiation of the investigation. The IRB, with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation, must find and document whether the investigation satisfies the approval criteria.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the emergency research criteria or because of other ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the investigator and to the sponsor of the clinical investigation. The sponsor of the research project must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

9. Additional Community Consultation Information

Community consultation activities should be designed to help ensure that the communities in which the emergency research will be conducted and from which subjects will be drawn

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are adequately informed about the risks and expected benefits of the research are given the opportunity to ask questions about it, and express their views prior to the IRB making a determination about the research. Community input is important to address perceptions and concerns associated with the study, product or the standard of care and may result in additional safety measures in the protocol. Community consultation also provides an opportunity to provide the community with people to contact if community members have concerns or would like additional information.

Suggested community consultation events:

- Standing meetings, such as local civic public forums, may be better attended because such meetings are already on community members' calendars.
- Public community meetings or other special meetings specifically organized to discuss the research. Such meetings may be valuable in attracting participation from individuals with strong interest in the research.
- Local radio and/or television talk shows; such programs allow viewers to "call in" to express their views and concerns.
- Interactive websites, focus groups and surveys.

At a minimum, the content of community consultation should include:

- A summary of the research protocol, study design, and a description of the procedures to be followed, including the identification of any procedures which are experimental;
- A summary of other available treatment options and what is known about their risks and benefits;
- An estimate of how long the study will last and expected duration of the subject's participation;
- How potential study subjects will be identified;
- Information about the test article's use, including a balanced description of the risks and expected benefits and any relevant information that is known about adverse events;
- A clear statement that informed consent will not be obtained for most research subjects;
- The rationale as to why the study must be conducted using an exception from informed consent;
- A copy of the informed consent document;
- Relevant information that would be part of the informed consent process (21 CFR 50.25(a) and (b), as applicable), e.g., available treatments for the condition under

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study; risks/potential benefits of participating in the research; possibility that FDA might inspect the subject's records;

- A description of the therapeutic window, during which the test article must administered, and the portion of that window that will be used to contact the subject's LAR;
- A description of the attempts that will be made to contact the subject's LAR to obtain consent, or, if no LAR is available, a family member to provide an opportunity to object to the subject's enrollment in the study, both before and after the test article is administered;
- A description of the way(s) in which an individual may express his/her desire not to participate and avoid involvement as a subject in the research (e.g., opt-out mechanisms), if any will be made available.
    - "Opt-out" mechanisms (i.e., ways for an individual to indicate a desire to not participate in research involving an exception from informed consent) are not required
    - Individuals in the community may ask about opt-out mechanisms, including, for example, providing individuals with a wallet card or medical bracelet that contains a statement that the individual does not want to participate in research. Electronic opt-out and registry systems may allow tracking of the excluded community members as well. Information about available opt-out mechanisms should be part of the public disclosure materials.

Public disclosure is also required in addition to community forums (1) before the emergency research may begin and (2) after the research has been completed. The IRB must find and document that public disclosure has occurred.

Examples of disclosures:

- Targeted mailings to households in the communities, with information about how to obtain further details;
- Advertisements and articles in the English language, and if appropriate, foreign language, newspapers (Public outreach documents should be translated into languages that are common in the area served by the facility where the investigation is being conducted and in the communities from which subjects will be drawn.);
- Clearly marked links and information on the sponsor's and participating hospitals' Internet web sites;
- Summary materials that are accessible to non-English speaking or homeless
- populations who reside in the community from which research subjects are likely to be drawn;

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- Presentation or distribution of information at meetings of community, local government, civic, or patient advocacy groups;
- Letters to local and regional community leaders and first responders (e.g., police, paramedics);
- Announcements to local/regional hospital staff(s);
- Public service announcements and interviews or discussions on "talk" radio or television programs;
- Press conferences and briefings; and
- Meetings or activities provided by hospitals' and institutions' existing community outreach programs may serve as both community consultation and disclosure.

REFERENCES

21 C.F.R. Part 50 – Institutional Review Boards

21 C.F.R. § 50.24(a)(7)(ii) and (iii)

21 C.F.R. § 56.115(a)

21 C.F.R. § 812.30 – Investigational Device Exemptions

31 C.F.R. § 312.30 – Investigational New Drug Application

45 C.F.R. Part 46 – Protection of Human Subjects

FDA Guidance "Exception from Informed Consent Requirements for Emergency Research" (Mar. 2011, updated Apr. 2013)

OHRP Guidance "Planned Research in Emergency Settings with Waiver of Consent (last updated June 9, 2016)

Ohio State University IRB

Mayo Clinic IRB

S. Mawocha, "Utilization of opt-out registries in Emergency Clinical Research," EMU 1-2011

B. HUMANITARIAN USE DEVICE (HUD)

A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals per year in the United States. Use of an HUD in clinical practice is similar to both research and regular patient care. The use of a HUD does not constitute research unless the physician or health care provider intends to collect data from its use. However, like research, the IRB must review and approve the use of the HUD. These devices do not undergo the same stringent requirements that investigational devices do, yet they may be

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the only recognized approved standard of therapy. This is the only situation where federal regulations require the IRB to approve and monitor an activity that is clearly not research.

By way of background, regulations provide for the submission of a Humanitarian Device Exemption (HDE) in which the manufacturer is not required to provide the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose prior to marketing. This regulation was developed to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. When the manufacturer submits the HDE, it must provide sufficient information in order for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury to the patient and that the probable benefits to health outweigh the risk of injury or illness from its use.

1. Definitions

Humanitarian Use Device (HUD) - a medical device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals per year in the United States.

Humanitarian Device Exemption (HDE) – FDA approval for a physician to use an HUD in clinical treatment or investigation. An approved HDE authorizes the marketing of a HUD. A HUD may only be used in facilities that have established local IRB review to supervise clinical testing of devices and the IRB has approved the use of the device to treat or diagnose a specific disease.

Use – When unmodified, this refers to the use of the HUD only according to its approved labeling and indications to treat or diagnose patients.

2. Physician Responsibilities for the Use of a HUD

A physician may utilize a HUD when agreeing to the following:

- The HUD will be used for treatment, diagnosis, or research in accordance with the labeling of the device, intended purpose, and in the designated population for which the FDA approved its use;
- The patient must be informed that the HUD is a device authorized under federal law for use; however, the effectiveness of the device for a specific indication has not been demonstrated; and
- The informed consent of the patient (or the patient's LAR) will be obtained when the use of the HUD involves research or when required by the IRB. The IRB generally requires that treating physicians obtain a device related surgical informed consent. However, a specific IRB-approved device consent is not federally mandated.

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- CITI HUD Module is required in addition to Health Information Privacy Security and Conflict of Interest prior to IRB approval being granted.

3. IRB Responsibilities

a. *Initial and Continuing Review of a HUD*

A HUD may only be used in facilities that have established IRBs constituted and acting in accordance with FDA's regulations governing IRBs, including responsibility for continuing review of use of the device. For initial review of a HUD, full committee review is required. For continuing review, however, an IRB may use the expedited review procedures, unless the IRB determines at the fully convened meeting that full committee review is necessary. IRB review and approval is required at least annually.

b. *IRB Approval of HUD Use*

A HUD may only be administered to, or implanted in, a patient located at a facility if such use has been approved by the IRB. IRB approval of the use of a HUD cannot exceed the scope of the FDA approved indication(s), but may limit the scope of the FDA approved indications if the IRB feels such limitation is appropriate. The IRB reserves the right to limit such FDA approved indications when appropriate. For example, the IRB may limit use of the HUD to a particular medical specialty, prior use and failure of any alternative treatment modalities, and/or reporting requirements to the IRB or IRB chair. Typically, approval of the HUD is for the facility. Medical staff must:

- Complete an application for each physician(s)
- Verify competency requirements
- Complete CITI HUD education requirements

The IRB does not require review/approval of each individual use of a HUD as long as the use of the HUD falls within the FDA approved indication and IRB limitation(s), if applicable. HUD uses and summary of patient experience must be reported to the IRB at the next continuing review of the HUD.

c. *Clinical Informed Consent for Use of a HUD*

IRB approval of a device specific research informed consent is not required before a HUD is used because an HDE provides for temporary marketing approval and does not constitute research. Nevertheless, the IRB requires that at least the informed consent form used for the surgical procedure, including the HUD specific patient information packet, be signed by the patient prior to use of the HUD. Best practice includes the addition of an IRB stamped approved HUD specific informed consent form for patients to consent prior to insertion. If the HUD is being used in an emergency situation, the patient information is provided following the procedure.

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4. Procedures

a. *IRB Submission Requirements for Use of a HUD*

Regardless of the intended use, a HUD requires prospective IRB review and approval by the full Committee. The use of a HUD does not constitute research unless the physician or health care provider intends to collect data from its use. At UCHealth, the healthcare provider credentialed for use of a HDE is a physician. A physician may insert and utilize a HUD. The physician must submit an IRB Application for review at a convened meeting. All potential users within the facility must be listed as additional physicians on the application. The primary physician must include the following information in the application:

1. The HUD product labeling, clinical brochure, and/or other pertinent manufacturer informational materials, including patient education materials;
2. The FDA HDE approval letter;
3. Written clinical use statement(s) from the physician/health care provider specifying how the HUD will be used at (i.e., who will be administering/implanting the HUD, for what clinical indication(s), etc.). The(se) statement(s) must specify that the use of the HUD will be limited to the clinical indication(s) listed in the FDA- approved product labeling;
4. Training and competency requirements per the labeling need to be provided to the IRB; and
5. HUD Consent Form. With the exception of emergency use, the consent form will address the proposed clinical use of the HUD. The HUD consent form should at a minimum, include the following information:
    - A description of the HDE/HUD approval process.
    - A description of the HUD and how the HUD will be used in the clinical setting. This information can be obtained from the FDA HDE Approval Letter and/or the HUD device labeling, clinical brochure, and/or other manufacturer informational materials and any IRB limitations. Based on this description, it should be clear to the patient why he/she is a candidate for the use of the device.
    - A discussion of possible risks, side effects, and/or adverse events associated with the HUD and its proposed clinical use;
    - A discussion of the possible benefits associated with the clinical use of the HUD;
    - A discussion of any alternative treatments or procedures (if any) that the patient may wish to consider in lieu of clinical use of the HUD;

- Voluntary consent statement(s) with patient signature and date of signature; and
- Physician/health care provider signature and date of signature.

b. *Continuing Review Requirements*

The physician is responsible for fulfilling continuing review requirements to the IRB at least annually. At the time of continuing review, the physician must report the HUD activities for the previous year. In addition, the following information must be provided to the IRB in summary form for each HUD at UCHealth or affiliated sites. This report must include the following:

1. A renewal application submitted by the responsible physician/healthcare provider (or designee) requesting continuation of IRB approval of the HUD. The application should identify the HUD, specify the clinical use statement(s) of the HUD, and, if applicable, summarize any known FDA action(s) taken regarding the HUD since last initial or continuing review;
2. A copy of the current FDA-approved product labeling for the HUD;
3. A copy of the current clinical informed consent form;
4. For each patient in whom the HUD has been used provide a summary of subject progress, tolerance, or problems.

5. Adverse Events and Unanticipated Problems

FDA regulations require that if a physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that a HUD has or may have caused or contributed to the death or serious injury of a UCHealth patient, whether expected or not, he or she must report such findings (using FDA form 3500A available on the FDA Medwatch site) to the FDA as soon as possible, but no later than 10 working days after the Investigator first learns of the effect or problem.

FDA regulations define a HUD serious injury or illness as the following:

- Life threatening
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

In the event of a related death, a report must also be made to the IRB within 24 hours of learning of the death. If the device malfunctions during deployment there is State of Colorado required reporting in addition to the IRB and FDA. This reporting is in addition

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to, not a substitute for, FDA and/or manufacturer reporting requirements. Contact Risk Management for assistance.

6. Prompt Reporting of FDA Action(s) on the HUD

The physician who requested use of the HUD must promptly report to the IRB any FDA action(s) taken regarding the HUD for which he/she has become aware. This report, which could be a copy of FDA correspondence with a cover letter, must be forwarded to the Chair within 10 days of receipt of such FDA action. Depending on the FDA action taken, the IRB Chair may elect to initiate an immediate IRB action (e.g., withdraw IRB approval of use of the HUD because FDA rescinded the HDE due to the availability of a comparable device) or await action until the full IRB has discussed the FDA action taken on the HUD (e.g., modifying the clinical use of the HUD because FDA has done so). Any immediate action taken by the Chair of the IRB will be discussed and voted on at the next IRB meeting.

7. Modifications to the HUD or the Clinical Use of the HUD

IRB approval is required for any modifications of the HUD and/or of the proposed clinical use(s) of the HUD. A physician requesting modification to either the HUD or the clinical use(s) of the HUD must submit one copy of the following:

1. A cover letter signed by the responsible physician describing the modification to the HUD and/or the proposed clinical use(s) of the HUD and the rational for such modification(s);
2. A copy of the HUD manufacturer's amendment to the HUD product labeling, clinical brochure, and/or the pertinent manufacturer informational materials corresponding to the requested modification(s);
3. A copy of any FDA HDE amendment/supplement approval letters; and
4. A copy of the revised clinical use statement(s) and clinical consent form with the modifications highlighted.

8. Investigational Use

When the investigational use of a HUD is according to its approved labeling and indications, the HDE holder may collect safety and effectiveness data for the HDE approved indication without an IDE. The investigator must obtain IRB approval.

When the investigational use of a HUD is beyond its approved indication (new indication), an investigation of the HUD must be conducted in compliance with the IDE regulations. The investigator must obtain IRB approval for investigational use [research] as they would for any device research protocol. The IRB will need to make a SR/NSR determination, unless already determined by FDA.

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C. EMERGENCY USE OF AN UNAPPROVED DRUG OR DEVICE

1. Emergency Situations

IRB review and approval must be obtained before an unapproved drug or device is used. There is an exception for emergency situations in which a physician in an emergency situation determines that IRB approval for the use of an unapproved drug or device cannot be obtained in time to prevent serious harm or death to a patient. In this case, an unapproved drug or device may be used without prior IRB approval to treat the patient provided that:

- The patient has a life-threatening condition that needs immediate treatment;
- No standard acceptable treatment for the condition is available; and
- Because of the immediate need to use the device, there is no time to obtain prior IRB approval or to use existing FDA approval procedures for the use.

2. Physician Responsibility in Emergency Use Situations

The treating physician should ensure that the following patient protection measures are followed before and after the emergency use occurs.

Before the emergency use occurs, the physician should obtain the following if possible:

1. Concurrence of the IRB Chairperson;
2. Informed consent from the patient or his/her legal representative;
3. An independent assessment by an uninvolved physician; and
4. After the emergency use occurs, the treating physician must submit a follow-up report to both the IRB on the patient's condition and information regarding the patient protection measures that were followed.
5. If the emergency use involves an HUD, the treating physician must also obtain authorization from the HDE holder before emergency use of the HUD. The physician must also submit a follow-up report to the HDE holder (in addition to the IRB) on the patient's condition and information regarding the patient protection measures that were followed.

In any case, the physician must (within 5 days after the use of the unapproved drug or device) provide written notification to the Chairperson of such emergency use of the unapproved drug or device. Written notification must include identification of the patient involved, the date on which the unapproved drug or device was used, and the reason for the use.

D. EXPANDED ACCESS (COMPASSIONATE USE OF AN INVESTIGATIONAL DRUG OR DEVICE)

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Expanded access refers to the use of an investigational drug or device in situations *outside of a clinical trial* to treat a patients that have a serious or immediately life-threatening disease or condition who lack other therapeutic treatments. Expanded access use of an investigational drug or device generally allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the drug or device may provide a benefit in treating and/or diagnosing their disease or condition. Use can be in individual patents, including in emergencies, intermediate size patient populations, and larger populations under a treatment protocol or treatment IND.

To permit treatment of a patient under the expanded access program, the following criteria must be met:

1. The patient's condition and the circumstances are life-threatening or serious, necessitating treatment with the drug or device;
2. There are no generally acceptable alternative therapies for the condition;
3. Patient does not meet the inclusion criteria in the clinical investigation;
4. Potential patient benefits justify the potential risks of the treatment;
5. Providing the investigational drug or device will not interfere with the trials that could support such drug or device's development or marketing approval for the treatment indication.

In addition, the physician should ensure the following:

1. That sponsor approval of expanded use in a Letter of Authorization is obtained prior to its use;
2. Ensure that IRB approval of expanded access is obtained prior to its use (except when FDA authorizes emergency expanded access use);
3. That FDA approval of expanded access is obtained prior to its use;

If there is an IND or IDE, as applicable, the physician should work with sponsor to submit an IND or IDE supplement (and all requisite documentation) requesting approval for expanded access use in order to treat the patient.

If there is no IND or IDE, as applicable, physician should work with the sponsor to submit the requisite information requesting approval for expanded access use in order to treat the patient, along with a description of the device as provided by sponsor.

If the FDA approves the expanded access request, the physician shall devise an appropriate schedule for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the drug or device and the specific needs of the patient. The physician shall report any problems as a result of the drug or device to the IRB and Sponsor.

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21 C.F.R. 312 Subpart I

Expanded Access to Investigational Drugs for Treatment Use-Questions and Answers, U.S., FDA, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expanded-access-investigational-drugs-treatment-use-questions-and-answers

Expanded Access for Medical Devices, U.S., FDA, https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/expanded-access-medical-devices

FDA Guidance for Industry: Individual Patient Expanded Access Applications: Form FDA 3926, June 2016

Expanded Access Information for Physicians, U.S., FDA, https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors

E. ADDITIONAL INFORMATION ABOUT OFF LABEL USE

Physicians should be cognizant that FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s). If a physician wants to use a HUD outside its approved indication(s), FDA recommends that the physician obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs and the limited information available about the risks and benefits of the device. FDA further recommends that the physician submit a follow-up report on the patient's condition to the HDE holder and first check with the IRB before such use to review any institutional policy. Medical Device Reporting reports must be submitted to FDA and to the IRB if the device may have caused or contributed to death or serious injury and for certain malfunctions.

REFERENCES

21 C.F.R. Part 56

21 C.F.R. Part 812

21 C.F.R. Part 814 Subpart H Humanitarian Use Device (Revised April 1, 2017)

Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors, U.S. FDA, https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors

FDA Guidance, Humanitarian Device Exemption (HDE) Program (September 6, 2019)

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Designating Humanitarian Use Device (HUD) (December 13, 2016)

Expanded Access for Medical Devices: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/expanded-access-medical-devices UCHealth Policy: Emergency Use of an Unapproved Research Device or Drugs Guidance

F. SIGNIFICANT AND NON-SIGNIFICANT RISK

The Investigational Device Exemption (IDE) regulations describe two types of device studies, "significant risk" (SR) and "non-significant risk" (NSR). A third type is exempt from IDE regulations. An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and:

- Is intended as an implant; or
- Is used in supporting or sustaining human life; or
- Is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A NSR device investigation is one that does not meet the definition for a significant risk device. NSR device studies, however, should not be confused with the concept of "minimal risk," as used in the IRB regulations to identify certain studies that may be approved through an expedited review procedure. IRB approval during a convened meeting of the IRB is required prior to conducting clinical trials and continuing review for both SR and NSR device studies. In addition, informed consent must be obtained for either type of study.

1. Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies must follow all of the IDE regulations. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated IDE regulations. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves as the FDA's surrogate for review and approval of NSR studies. Once the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that a SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

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If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination.

2. IRB Considerations

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

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

3. IRB and Sponsor Responsibilities Following SR/NSR Determination

If the IRB decides the study is Significant Risk:

- The IRB must notify sponsor and Investigator of SR decision. SR device studies must follow all the IDE regulations, including FDA IDE application approval. After IDE is obtained by the sponsor, review of the study applying the requisite criteria may proceed
- The Sponsor must submit IDE to FDA or, if electing not to proceed with study, notify FDA of the SR determination. The study may not begin until FDA approves IDE and the IRB approves the study. Sponsor and investigator(s) must comply with IDE regulations, as well as informed consent and IRB regulations. There is no requirement for the sponsor to notify FDA of the SR determination. The sponsor must provide to the IRB the IDE number and/or copy of the IDE approval letter when requested.

If the IRB decides the study is Non-Significant Risk:

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- The IRB proceeds to review study applying requisite criteria
- If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements", and informed consent and IRB regulations. Abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports and prohibition against promotion. There is no requirement to make progress reports or final reports to the FDA.

4. The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study.

To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, NSR studies qualify as minimal risk, and the IRB may choose to review those studies under its expedited review procedures.

5. IRB Documentation

The IRB should document its decision in the meeting minutes. The minutes should describe the IRB's reason for its SR or NSR determination and may also include the documentation used to establish the IDE status for the study. For an SR determination, such documentation may include, for example, a copy of the IDE approval or conditional approval letter from FDA. For a NSR determination, the documentation may include FDA's NSR determination as available. FDA will issue a NSR letter upon written request.

6. Exempt from IDE Requirements

For studies that are exempt from the IDE regulations, the IRB does not need to decide whether the study poses a significant risk or non-significant risk. However, the IRB must still review the study in accordance with the IRB regulations before the investigation may begin.

REFERENCES

21 C.F.R. Part 812

21 C.F.R. Parts 50 and 56

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Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies, U.S. FDA, http://www.fda.gov/oc/ohrt/irbs/appendixc.html

FDA Information Sheet Guidance on "Frequently Asked Questions about Medical Devices," http://www.fda.gov/oc/ohrt/irbs/appendixc.html

Significant Risk and Nonsignificant Risk Medical Device Studies; CDRH – FDA Guidance January 2006

CDRH Program Operations Staff 301-594-1190

VIII. INFORMED CONSENT

A. GENERAL REQUIREMENTS

Federal regulations require that informed consent be obtained before a human subject may participate in any clinical investigation. Informed consent is foundational to the ethical conduct of research. It is imperative that IRBs ensure participants are informed about the research protocol and voluntarily consent to participation prior to the initiation of any research procedures. Informed consent must be obtained from each participant and must be appropriately documented. However, informed consent is not merely an executed form, it is a process that involves giving subjects:

- adequate information concerning the study to provide understanding,
- an opportunity to consider all available options,
- a response to all questions, and
- a choice to voluntarily consent to participate.

Note that research involving vulnerable populations may have additional informed consent requirements. See Section VI.F.

1. Consent Process & Form Development

Informed consent must be legally effective and prospectively obtained. No Investigator may involve a human being as a research subject unless he/she has obtained informed consent of the subject or the subject's LAR (legally authorized representative). A subject's LAR is an individual, 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.

Consent shall be obtained only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate.

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Dialogue is a fundamental requirement of the informed consent process. The written consent form is simply an adjunct to the face-to-face interaction between the investigator and the subject. Nevertheless, the consent form must stand on its own as a comprehensible, informative, and forthright account of the dialogue that occurred.

The Investigator must ensure that the informed consent process is carried out appropriately. Because a participant may perceive pressure if his or her medical care provider is the Investigator, certain elements of the informed consent process may be delegated to properly trained research staff to minimize the possibility of coercion or undue influence. Prior to delegation, research staff should complete a performance competency.

Preparation of the consent form document is the responsibility of the Investigator, but the form is often developed by the sponsor or contract research organization and submitted by the Investigator/designee for review by the IRB. The IRB must review and approve the informed consent document before study implementation. Any changes made to the informed consent document after IRB approval must be submitted to and approved by the IRB prior to study implementation. If possible, the informed consent should have a preparation or revision date to ensure that the correct version is being used. If the informed consent document is changed during the course of the study, and the changes affect subjects currently enrolled, those subjects must be re-consented and sign the revised version.

Subjects must be provided adequate time to read and review the consent form prior to signing it. Ideally, the subject should be allowed to take a written copy home to read and discuss with family prior to signing. The consent process should occur in a quiet, private area so the subjects do not feel intimidated. They must be given an opportunity to ask any questions they have concerning the study.

The subject or the subject's LAR must sign and date the informed consent. The subject must be provided with a copy of the informed consent. The person who conducted the informed consent discussion should also sign and date the form. The subject and/or the subject's LAR should receive a copy of the signed and dated written informed consent document.

2. The Consent Form

The Consent Form may be either of the following:

- A written informed consent form that meets the requirements of informed consent listed in subsection 3 below. The Investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form themselves before it is signed, or alternatively, this form may be read to the subject or the subject's LAR. Optimally, the form may be taken home before the research process begins to allow time to read and outline as needed. The subject must also be given a copy of the signed form to keep.

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- A "short form" written informed consent form stating that the elements of required informed consent have been presented orally to the subject or the subject's LAR, and that the Key Information was presented first to the subject, before other information, if any, was provided (see 3. Below). When this method is used, there shall be an impartial witness to the oral presentation who is not a research associate or a family member. The IRB must approve a written summary of what is to be said to the subject or representative.

The original, signed informed consent form should be kept in secured research files for at least six years.

3. Requirements for Informed Consent

- **Key information to be presented first (Key Information)**: A concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

  Note: Research that is not subject to 45 CFR Part 46 does not require Key Information but may include it.

- 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 this information.
- 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 LAR's understanding of the reasons why one might or might not want to participate.
- A statement that the study involves research, an explanation of the purposes of the research, 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 that may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.

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- A statement describing the extent to which, if any, confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- 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, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- For research subject to 45 CFR Part 46, 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.
- The following statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.Gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

4. Additional Requirements

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

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

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- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's or LAR's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new 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.
- The approximate number of subjects involved in the study.

For research subject to 45 CFR Part 46—

- 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 and whether the subject will or will not share in this commercial profit.
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
- 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).

5. Other Considerations

- Second Person: The language of the consent documentation should convey a dialogue with information being provided. The information provided should provide evidence that there is a choice to be made by the subject rather than presumption of the subject's consent with the use of the first person style.
- Simple Language: The information provided in the informed consent documents must be in language understandable to the subject. The informed consent document should not include complex language that would not be understandable to all subjects. Technical and scientific terms should be adequately explained using common or lay terminology.
- Exculpatory language: Informed consent documents may not contain any language through which the subject is made to waive or appear to waive or legal

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rights or releases or appears to release the Investigator, the Sponsor, or UCHealth from liability for negligence. Subjects may be required to give up rights to biospecimens. For example, it is acceptable to include language such as "you will give up any property rights you may have or you will voluntarily and freely donate biospecimens."

- FDA-Regulated Test Articles: For all research involving test articles regulated by the FDA, informed consent documents must include a statement that the purpose of the study includes evaluation of the safety and the effectiveness of the test article. The consent form must also include a statement that the FDA has access to the subject's medical records.

6. Non-English Speaking Participants

Individuals who do not understand English may ask or may be asked to participate in a clinical trial. The investigators and IRB should consider the ethical ramifications of enrolling or excluding potential participants when a language barrier may exist between the investigators and some or all of the potential participants. Individuals should not be routinely excluded from research only because they do not speak English.

When participants who do not speak English are enrolled in a study, consent must be obtained in a language the subject can understand. The IRB must review and approve all English and non-English language versions of any consent documents (long form or short form with a written summary) that will be used by investigators to document the informed consent of participants. When investigators reasonably expect that the subject population for a proposed study will include individuals who do not understand English and can anticipate the specific language(s) that they will understand, the investigator should submit to the IRB, prior to its final review, appropriately translated consent documents, along with a description of how interpreters for oral communication will be made available during the research. The expedited review process may be used for the short form and for certified translated versions of the informed consent document.

If a written translated informed consent form is not available, and there is not enough time to submit properly translated consent documents to the IRB for review, then a verbal translation process is required and the following process should be followed:

- Determine whether there is sufficient justification to enroll the subject without using a translated long form to document the participant's consent (e.g. limited therapeutic window). The Investigator (and IRB Chairperson or designee, when feasible) should consider whether the consent process will provide the subject with sufficient opportunity to understand the information. If the investigator believes that the prospective participant has not understood the information, then the individual should not be enrolled in the study.
- Obtain and document the participant's informed consent using a translated short form, along with the English language version of the long form and written

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summary. To meet this step, the IRB must have approved the use of such translated short forms, as well as a written summary of what is to be said to the prospective participant. The IRB-approved long-form can be used as this summary. The investigator should obtain consent using the following process:

- The investigator, using an interpreter if necessary, orally provides the elements of informed consent and any additional pertinent information in the IRB-approved version of the long form. This presentation may be an oral translation of the IRB-approved English version of the long form. The investigator, through an interpreter if necessary, will answer any questions from the proposed participant. There must be an impartial witness to the oral presentation who is not the person obtaining informed consent or a family member. The witness should be someone who is fluent in the language of oral presentation and the language of the subject.
- At the time informed consent is sought, the participant is given the IRB-approved translated short form and a copy of the IRB-approved English version of the long form, which serves as the written summary.
- The short form must be signed and dated by the participant.
- The witness must sign both the short form and the copy of the IRB-approved English version of the long form. The witness should be someone who is fluent in the language of oral presentation and the language of the subject. Interpreters may serve as a witness, however, UCHealth Translation Team members should not serve as a witness. If the company providing interpretation services do not permit their interpreters to act as witnesses, the interpreter should only act in the role of interpreter, and another individual should serve as the witness.
- The person actually obtaining consent signs the copy of the IRB-approved English version of the long form.
- A copy of the English version of the long form must be given to the subject (or subject's legally authorized representative), in addition to copy of the short form.

After the participant has been enrolled in the study, the investigator should take the following additional actions:

- If the participant was enrolled without waiting for a translated long form to be approved by the IRB and the investigator did not consult with the IRB Chairperson or designee prior to the participant's enrollment, the investigator should promptly notify the IRB Chairperson or designee that the participant was enrolled.
- The investigator should promptly obtain a translated copy of the IRB-approved English version of the long form. The translated form should be submitted to the

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IRB for review and approval. After the translated long form is approved, the investigator should provide the form to the participant as soon as possible.

7. Illiterate Participants

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document, when consistent with applicable state law. A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended."

B. Documentation of Informed Consent

Each subject or his/her LAR must sign and date a copy of the current IRB approved consent form prior to enrollment or any participation in any phase of the study, unless the requirement is waived by the IRB. The subject must also be given a copy of the document to take with them. However, a signed document is best practice.

The IRB may approve procedures for documentation of informed consent that involve (a) a written consent form signed by the subject; (b) a short form written consent form with oral presentation; or (c) in limited circumstances, waiver of signed written consent form. Each of these three options is described in detail below. It is the responsibility of the IRB to determine which of the procedures described below is appropriate for documenting informed consent in protocols that it reviews. Generally, option (a) is recommended. Refer also to Section VIII.C Waiver of Informed Consent.

1. Oral Presentation Using Short Form

Oral presentation using short form is recommended for subjects who do not speak English when a written translated consent form is not available. Please refer to Section VIII.A.5.

2. Observation and Monitoring of the Informed Consent Process

There may be circumstances that arise under which the IRB may want to observe the consent process. For example, at the time of initial protocol review, the Board may determine that although the risk/benefit determination allows for consenting of potentially cognitively impaired adults, additional safeguards must be instituted to protect the rights and welfare of subjects. In this situation, the IRB may delegate the administration or

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observation of the consent process to a qualified third party. Observation and monitoring will be initiated for routine auditing and for causal investigations.

3. Decisional Impairment

Informed Consent for studies involving subjects who are decisionally impaired may take place over extended periods of time. The IRB should consider whether periodic re-consenting of individuals should be required to ensure their continued involvement is voluntary. Additionally, the IRB should consider whether, and when, it should require a reassessment of decision making capacity. Assent processes may be required in instances where the subject is not legally capable of giving informed consent (e.g., minors) or where the subject is cognitively impaired.

4. Use of Facsimile, Email or Mail to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by mail, or secure email or facsimile to the potential subject or the potential subject's LAR and to conduct the consent interview by telephone when the subject or the LAR can read the consent document as it is discussed. This process is not optimal and is reserved for unique circumstances. Refer also to Section VIII.C Waiver of Informed Consent and Telephone Consent Guidance.

C. Exemptions and Waivers of Written Informed Consent

An IRB may waive or alter the requirements for informed consent only if it finds and documents:

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

In most cases, a potential research subject must be given a full explanation of the IRB approved protocol and be given the voluntary choice to participate without coercion. An individual's agreement to participate must be documented on an IRB approved consent form unless a waiver is granted. The Department of Health and Human Services has developed special rules permitting an IRB to approve, under limited circumstances, a consent procedure, which does not include, or which alters some or all of the elements of informed consent, or waives the requirement to obtain informed consent if the IRB finds that the research meets certain criteria.

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FDA regulated research is recently eligible for a waiver or alteration of consent, effective July 25, 2017. (This is a change from the previous limitation of applicability for emergency use of a test article under 21 C.F.R. Part 50.23 or planned emergency research under 21 C.F.R. Part 50.24.)

When granting a waiver, it is important for the IRB to consider the potential subjects and whether a waiver would be objectionable, cause harm or have adverse consequences. Religious, cultural, or tribal believes should be considered as well.

1. Definitions

Minimal Risk – To satisfy the definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an estimate of "the harms and discomforts ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests." Waivers will be granted only for those protocols with minimal risk or less.

Practicable - The commonly accepted definitions of the term "practicable" are (a) feasible; (b) capable of being effected, done or put into practice; and (c) that may be practiced or performed; capable of being done or accomplished with available means or resources.

Practicality should not be determined due to researcher convenience, cost or speed. Practicably refers to feasibility or the capability of the research being accomplished with available means or resources. The following concepts may help to determine if research could not practicably be carried out without a waiver:

- Scientific validity would be compromised if consent was required.
- Sample size is so large that consent may cause bias (e.g. data sampling or population based studies as in epidemiologic studies).
- Record reviews that may be older (20 years) where large numbers of subjects are lost to follow-up or have died.
- There is a risk of psychological, social, or other harms by contacting individuals or families (e.g. victims of violent crimes or traumatic injuries).
- Disclosure of study purpose would bias subjects (e.g. description research).
- A risk of privacy disclosure is greater than the research itself (e.g. re-identifying coded/linked information).
- Ethical concerns would be raised if consent were required. For example:
    - There is a risk of creating additional threats to privacy by having to link otherwise de-identified data with nominal identifiers in order to contact individuals to seek consent.

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- There is a risk of inflicting psychological, social or other harm by contacting individuals or families.

Whenever Appropriate – This standard applies when subjects must be provided with additional pertinent information after participation because it is ethically required or respectful to provide the subject with such information after the research is complete. The IRB may require this mechanism when subjects are included in so-called "deception research," in which some aspects of the study are not fully disclosed upfront so that subject responses are not biased. While the IRB must consider if this applies each time a waiver is reviewed, not all protocols with an informed consent waiver are required to provide additional information to subjects after their participation. Under most circumstances, this standard does not apply to retrospective research conducted under a waiver (e.g. record review).

2. Exemptions or Waivers of One or More Requirements of Informed Consent

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

- **For General Research:** the research involves no more than minimal risk to the participants and, the waiver or alteration will not adversely affect the rights and welfare of the participants, the research could not be practically carried out without the waiver or alteration, and, whenever appropriate, the participants will be provided with additional pertinent information after participation. The most common example of this situation is retrospective record review where PHI is used but not disclosed. The researcher must de-identify and securely store the information. In most cases, it is not necessary to provide the subject with any pertinent information because there is no deception.
- **For Public Benefit or Service Programs**: the research could not be practicably be carried out without the waiver or alteration and the research or demonstration project is to be conducted by or participant 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 program or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.
    - Note that this criterion applies to research activities that are under state or local authority; research activities conducted by or subject to approval of a federal authority or private entity would not qualify under this.

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- **Planned Emergency Research:** The IRB can approve a waiver of the requirements for informed consent for non-exempt research in life-threatening situations in which it is not possible to obtain informed consent from subjects or their LARs. See Section VII.A – Planned Research in Emergency Setting.
- **Research Designed to Study Conditions in Children:** The IRB can waive or alter the requirements for parental or guardian permission for certain minimal or less than minimal risk, non-exempt research involving children. Please refer to Section VI.G.3.e addressing the consent requirements for research involving children.

Additional Requirements and Limitations:

- The study team has provided a sufficient explanation as to why the study meets all of the four criteria listed above.
- The IRB documents its findings justifying the waiver or alteration of consent.
- Alteration or Waiver of One or More Elements of Informed Consent

An IRB may approve research for which some or all of the elements of informed consent have been altered, or for which some elements have been left out. For example, some research designs require that the subject be left unaware of the particular purpose of the research, because the subjects' responses might be biased if they know in advance what the investigators are looking for in the study. Such research designs do not preclude offering potential subjects some information about the research and giving them the opportunity to decide whether to participate.

The IRB may approve such research in which investigators will leave out or alter elements of informed consent, so long as the research meets the same criteria for approving research in 45 CFR 46.111, and the research meets the same criteria specified in the HHS regulations for leaving out or altering those elements as outlined above. [Reference: OHRP Informed Consent FAQ] The elements left out or altered must be clearly identified in the research application with purpose and minimal risk determination. The waived criteria should be delineated in the approval process and minutes. The alteration requires a protocol specific justification.

3. Waiver of Standard Informed Consent Documentation Requirements

The IRB may require the process of consent but waive the requirement for the investigator to obtain a signed consent form for some or all subjects only if the IRB finds and documents that:

- The only record linking the subject and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will

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govern (e.g. domestic violence research where the primary risk is discovery by the abuse that the subject is talking to a researcher); or

- The research (1) presents no more than minimal risk of harm to subjects (i.e. the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during routine examinations or tests), and (2) involves no procedures for which written consent is normally required outside of the research context (e.g. blood sampling or shopper surveys).

Some subjects might sign the consent form but refuse a copy of the consent form once signed out of concern that their possession of the form could compromise their privacy (for example an HIV study). This is consistent with the idea behind one of the reasons for a waiver of the requirements for documentation of informed consent – that harm would result to the subject if his/her identity were compromised by the documentation itself. The investigator may document that the subject refused a copy of the informed consent document and still include the subject in the study.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects, or the parents of children who are subjects, with a written statement regarding the research. When the IRB considers waiving the requirement to obtain written documentation of consent, the IRB reviews a written description of the information that will be provided to subjects via an oral consent script, contact letter, phone script or similar document. If a waiver of written consent is granted by the IRB, the IRB will determine whether the investigator must document the oral consent in research study files and/or the subject's medical record.

4. Waiver of HIPAA Authorization

Informed consent and HIPAA authorization waivers should have congruent approval processes.
The conditions of minimal risk, protection of subjects, and practicability all exist for HIPAA authorization waiver. HIPAA requires that the IRB find and document the elements in the following list when a waiver will result in use or disclosure of protected health information (PHI) in connection with the research projects. Any use or disclosure of PHI in connection with the research project involves no more than minimal risk to the privacy of individuals, as demonstrated by the following:

- There is an adequate plan to protect any identifiers from improper use or disclosure (e.g., they are kept in a locked cabinet only available to the researchers, or they are maintained in a password protected database and only the researchers have access to the password);

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- There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of research, unless there is a health or research justification for retaining the identifiers, or retention is otherwise required by law (e.g., there is a plan to break any links to identifiable information, unless the links need to be maintained, in which case a reason should be given); and

- There are 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 of disclosure of PHI would be permitted by HIPAA (e.g. "the information will not be used or disclosed for any purpose other than this specific research project").

- The research could not practicably be carried out without access to and use of the PHI.

The applicable waiver conditions will be delineated in the IRB approval determination. A waiver will be documented in continuing review documentation as "all conditions have been met" (unchanged).

REFERENCES

21 C.F.R. Part 50

45 C.F.R. §§ 46.116-46.117

Institutional Review Board Management and Function by E. Bankert, R Amdur 2nd Edition Section 6-1

Thompson Guide to Good Clinical Practice 430 Informed Consent http://www.thompson.com/members/libraries/fooddrug/clin/chap400/clin430.html?printer14-2012

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FDA Guidance Institutional Review Boards Frequently Asked Questions Informed Consent Process 34-53

FDA: A Guide to Informed Consent—Information Sheet

FDA Guidance: Exception from Informed Consent Requirements for Emergency Research

SACHRP Letter 1-31-08: Practicality should not be determined based on research convenience, cost or speed. Practicality refers to feasibility or the capability of the research being accomplished with available means or resources.

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects, July 2017

FDA Guidance: Exception from Informed Consent for Studies Conducted in Emergency Settings Informed Consent FAQ's OHRP 3.5.2018

IX. RESPONSIBILITY OF INVESTIGATORS

A. REVIEW OF RESEARCH

All human participants' research that is conducted by or under the direction of any employee, faculty, staff, student or agent of UCHealth in connection with his or her institutional responsibilities must be reviewed by the IRB.

B. INFORMATION SUBMISSION

1. Investigator Professional Qualifications

The investigator and/or designee shall submit documentation of his or her qualifications to do research to the IRB as a part of their initial protocol submission. Such documentation may include the following:

- Curriculum Vitae/Medical Staff Credentialing (updated and signed every two years)
- Degrees earned
- Licenses (current)
- Board Certification
- Statements of previous experiences or statements of qualification from other investigators
- Annual financial conflict of interest training and disclosure using CU Anschutz's process
- Verification of continued education in the areas of research and/or ethics. All researchers must provide proof of completion of research-related education. Completion of a research participant protection course is accepted. The web-based course Collaborative IRB Training Initiative

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(CITI) is offered free of charge to researchers. Researchers are required to complete the CITI training prior to application. Education records should be forwarded to the IRB office. Upon renewal, if education is not completed in 3 months, notification of non-compliance will be sent to the researcher and the IRB. If CITI has not been completed within 3 months, the investigator or research staff will be removed from all studies. Conflict of Interest Yearly Disclosure via CU Anschutz portal or CITI process, depending on affiliation.

2. Research Administration Review

Feasibility and budget review is the responsibility of the regional Research Administration department and is conducted prior to initiation of study. Any required credentialing/licensing verification is done by Medical Staff Services. This process is completed for both physicians and allied health personnel. Employees of UCHealth are evaluated for their research job description by their director.

3. Investigator Submission Requirements for Initial Review

Primary investigators must submit all required materials to the IRB with their application. IRB members rely on the documentation submitted by Investigators for initial and continuing review. Therefore, this material must provide IRB members with enough information about a study so that they may assess the adequacy of the protocol/project to meet the criteria for approval.

a. *Biomedical Research Protocol Submission Requirements:*

- Study Application Form, including contact information
- Research Protocol
- Investigator Brochure or Device Specifications
- Proposed Informed Consent document(s) including translated versions if applicable Data collection tools
- Any other supporting material, such as examples of recruitment advertising, posters, patient information, etc.
- IDE and/or IND numbers as appropriate
- COI disclosure statement

b. *Social-Behavioral Research Submission Requirements*

- IRB Application
- Study Summary Form or Project Summary
- Data collection tools
- Any other supporting material, such as examples of recruitment advertising, posters, patient information, assessment instruments, etc. (if applicable)

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- Proposed Informed Consent document(s) including translated versions if applicable

c. *Additional Requirements*

Purpose – The purpose of the study should be clearly stated. The risks and benefits to the subjects and the expected beneficial outcome of the study should be stated in quantifiable terms.

Sponsor – The name of the sponsor shall be clearly stated on the protocol. If the investigator is the sponsor, this fact should be clearly indicated in both the application and the protocol and conflict of interest statement.

Location – All UCHealth locations need to include details. If the investigator applicant proposes to use facilities other than UCHealth as a research location, a description of the facilities available and a safety plan for treatment of severe adverse reactions by the subjects must be addressed.

Previous Research – The investigator may submit with the application and protocol results of research previously conducted in the field of the proposed study. Such results may include:

- Current Journal articles or sponsor papers;
- Results of foreign studies;
- Written results of studies conducted elsewhere but not yet published; Subject inclusion and exclusion criteria

Vulnerable Subjects - Justification for inclusion of Vulnerable Subjects, if applicable.

Study Design

- Discussion of the appropriateness of research methods
- Description of the procedures to be performed
- Provisions for managing adverse reactions. (See Section VI.D)

Informed Consent - Procedures for documentation of informed consent, including:

- Assent, witnesses, translation and document storage;
- Circumstances regarding informed consent including setting, subject autonomy, language difficulties, and vulnerable populations;
- Compensation to subjects for participation; and
- Compensation for injury.
- (See Section VIII Informed Consent and Section VI.F – Vulnerable Subjects);

Privacy - Provisions for protection of subjects privacy, including HIPAA compliance

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Costs - Extra costs to the subjects for participation or extra costs to third party payers for subjects' participation

Continuing Review

- Investigators Brochure Request for changes to study after initiation,
- Unanticipated Problems (See Section VI.D.14), and
- Progress reports.

Final Report – Required for study completion. (See Section VI.G Study Completion)

Forms & Reports – Submit any other required institutional forms and reports

The IRB must receive these materials no later than three weeks prior to the IRB meeting to allow review of this material. A calendar of submission dates is provided to the investigator and their research teams at the beginning of each year or upon request.

d. *Inadequate Documentation or Information*

If the IRB or IRB staff determines that the submitted documents are not adequate, Investigators will be required to submit additional information. The IRB will not review incomplete submissions.

C. PRINCIPAL INVESTIGATOR QUALIFICATIONS

1. Principal Investigator (PI) Definition

An individual with the appropriate scientific and/or scholarly training and expertise to assume direct responsibility for the ethical conduct of a study involving human subjects. The PI prepares and carries out the clinical trial protocol or research paid for by the grant. The PI also analyzes the data and reports the results of the trial or grant research. PIs provide medical, technical and administrative oversight of the research and make important study-related decisions. The PI is responsible for selecting, training, and evaluating project staff, subject to the policies and procedures of the UCHealth IRB. If the study includes medical care (e.g. FDA-regulated drug or device protocols), then the PI must be a physician.

2. Assessing Competency

Sponsors must select Investigators who are "qualified by training and experience as appropriate experts" to investigate the test article. IRBs also review an Investigator's qualifications. In order to fulfill its responsibilities to ensure that risks to subjects are minimized and are reasonable in relation to anticipated benefits, the IRB needs information about the qualifications of the investigator(s) to conduct and supervise the proposed research.

In many cases, the IRB may have previous experience with an Investigator or institution that would allow it to readily determine if the Investigator is appropriately

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qualified to conduct and supervise the proposed research. The IRB should be able to obtain a statement confirming the Investigator's qualifications from the Medical Staff Services department. The IRB may also rely on Patient Care Services department or service line directors for validation of qualifications.

3. Validation of Research Qualifications

The IRB must validate the Investigator's qualifications, including the following:

- Education during initial schooling, internship, residency, or fellowship
- Training provided as a part of the protocol start-up meeting
- Online or other training programs
- Board certification (Certified Physician Investigator or CPI) with Academy of Pharmaceutical Physicians and Investigators
- Credentialing process for Medical Staff that insures compliance with Joint Commission on Accreditation of Healthcare Organizations requirements
- Past research experience

The IRB is not a privileging entity. The process through which physicians and other practitioners are granted clinical privileges and the process used to approve medical research in a hospital (i.e., the IRB) are two separate processes. Additional privileges are probably not needed if the activity calls for the practitioner's existing knowledge or skills, but physicians performing experimental procedures should request additional privileges via the medical staff office if necessary (e.g., procedure involves equipment or technology that is new to the institution, potentially hazardous, or requires new skills or training).

4. Additional Considerations

Evaluation of the investigator's qualifications should include the following indicators of experience that contribute to the research validation process (e.g., reviewing the curriculum vitae of the investigator, sub-investigators, and other necessary study staff; verifying professional association and medical licensure; reviewing relevant publications).

If the proposed research involves higher risks, vulnerable subjects, or novel technologies or surgical techniques, previous specific experience both in this field (as demonstrated by recent presentations or publications) and prior experience with the test article is required.

In addition, the IRB should pay particular attention to an Investigator's qualifications to conduct a study submitted for approval to the IRB if the study involves one or more of the following:

- An external investigator;
- A study that is outside of the investigator's area of expertise; or

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- Any study design features or other characteristic(s) that may significantly increase potential risks to subjects.

The IRB should be prepared to assess the adequacy of the facility's staff and equipment, including availability of emergency or specialized care if the need should arise. Past experience with similar equipment is a prerequisite for research involving medical devices and/or equipment.

REFERENCES

IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed (August 2013)

D. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The PI assumes complete responsibility for the ethical conduct of research conducted at UCHealth. Although they may delegate responsibilities, the PI has ultimate responsibility for adherence to the protocol, federal guidelines and UCHealth IRB policies and procedures. The ethical guidelines of the Belmont Report serve as a foundation for research practice. The entire research team is encouraged to read the Belmont Report to understand their ethical responsibilities in conducting research with human subjects.

1. Prior to conducting research:

Protocol - Research will be conducted according to the IRB approved research protocol. The sponsor, OHRP, FDA and UCHealth will hold the PI responsible, for properly conducting the research protocol.

Contract - For most research protocols including drugs and devices, a contract must be developed between UCHealth and the corporate sponsor. This contract must be approved by the Director of Research Administration and the Legal department. In addition to the PI's obligations under the contract, if a study is regulated by the FDA, the PI must comply with its obligations as outlined on the 1572 form.

Training - OHRP strongly recommends continued PI training both in research protection and the procedures of the protocol, as needed per the IRB. Collaborative Institutional Training Initiative (CITI) is a web based IRB educational program. CITI completion is required as a PI and Sub-I. All UCHealth research staff are required to complete CITI every 3 years. Completion fulfills the general research education requirement. For new PIs, the protocol will be on contingency hold until the training has been completed. The PI is also responsible for completing any training that is conducted by the sponsor.

Delegation - The PI may delegate the tasks and procedures regarding the study, but may not delegate the responsibility for proper conduct of the study. All of the actions of the Sub-Investigators and the research staff involved with the research are the responsibility of the PI. A plan must be developed, along with a delegation log, for the supervision and oversight of the research. Investigators should hold

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routine meetings with staff and monitors. There should be procedures for all aspects of the research protocol, including the following examples:

- Sponsor education and drug and device accountability
- Timely correction of errors, problems, deviations (Corrective Action Plans (CAP)
- Internal review/audit process
- Informed consent procedures
- Data reporting from source records (discrepancies)
- Adverse event reporting and analysis
- Action plans for medical and ethical issues

Conflict of Interest (COI) - The PI, Investigators and Research Team must disclose any existing conflicts of interest, they or their family members hold. UCHealth has decided that all researchers will abide by the conditions of the University of Colorado Denver (CU Anschutz) Financial Conflict of Interest program that requires annual reporting using the CU Anschutz system. Any reimbursement from the corporate sponsor, including travel or speaking fees, must be included in the disclosure. If applicable, any PI, Investigator, or member of a Research Team must follow the management plan agreed to by all interested parties and approved by the IRB. A new COI that arises at any point after the initial disclosure must be reported to the IRB (via an updated disclosure in the CU Anschutz system) within thirty days after the COI is realized. A study may be suspended or terminated at the discretion of the IO or the IRB if a PI, Investigator, or member of a Research Team fails to comply with this paragraph or fails to reasonably cooperate with any follow-up inquiry or request related to a disclosure made pursuant to this paragraph.

Sufficient Resources - An important part of the PI responsibility is to ensure that there are sufficient resources to conduct the study properly. These resources include:

- Qualified and trained staff that understand and carry out the plan, monitor and compile the research, and document all education and training sessions;
- Adequate facilities are available for the type of research being completed;
- A process to validate that all assisting staff fully understand the protocol and their duties within the research.

Recruitment

- Subjects may not be recruited or enrolled prior to the IRB's approval date, or after the expiration date of the IRB's approval. Data extraction may not begin until after the IRB approval date.

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- All recruitment materials, in any form of media, must be approved by the IRB prior to use.
- All materials that will be viewed by patients must be submitted for review. They will be date stamped as appropriate.
- Finder's Fees are not appropriate. Any payment connected to stimulating recruitment should be refused.

Informed Consent Form

- The PI is responsible for obtaining and documenting the signed and dated informed consent. This responsibility may be delegated to appropriately trained staff if documented in the delegation log.
- The consent form must be the most current UCHealth IRB approved and dated form.
- The language used orally and in written format during the consenting process needs to be non-technical and practical to allow better understanding by the subject and the subject's LAR.
- A potential subject must be provided with sufficient opportunity and ample time to decide whether or not to participate in the research study during the consent process. IT is recommended that a copy of the informed consent form be given to the subject prior to the consenting process
- The consent form should be signed by the person obtaining consent.
- Original signed informed consent form should be kept in secured research files for at least 6 years.
- A signed copy of the informed consent form must be sent to Health Information Management (HIM) to be added to the subject's medical record.

HIPAA Authorization

A HIPAA Authorization will need to be obtained prior to enrolling or reviewing any PHI.

- All research authorization documents must be reviewed and approved by the UCHealth IRB who serves as the privacy board.
- All subjects must be given signed and dated copies of the authorization.
- Keep the originals in secured research files for at least six years.
- A signed copy of the authorization must be sent to Health Information Management (HIM) to be added to the subject's medical record.

2. Conducting research

The IRB has the authority to approve, approve with conditions, or deny approval of protocols. If the study is approved with conditions or is in a suspended status,

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there will be NO enrollment of new subjects until the contingency or suspension issue is satisfied.

- Continuing Review: The IRB must review and approve all research protocols and informed consent forms at intervals appropriate to the degree of risk, but no less than once per year. **There is no grace period if renewal is missed.** Prior to the date on which the IRB approval of the research expires, the IRB will send a reminder to submit a renewal form. Review the IRB meeting and submission schedule. PIs may need to submit the renewal 45-60 days before the expiration based on meeting dates. Although the IRB sends reminders, it is ultimately the PI's responsibility to submit the renewal in a timely fashion to ensure that there is not a lapse in approval dates.
- Expired Approval: If IRB approval of a study expires before continuing review and approval occurs, investigators must stop all research activities that relate to that study. If the IRB judges that it is in the best interests of already enrolled subjects to continue to participate, the PI must obtain permission from the IRB. The IRB will determine if activities should continue or stop completely.
- Changes to Protocol: A revision or change to the protocol may also be referred to as an amendment, addendum or update. A revision must be submitted to the IRB by the PI or designee to change any aspect of the research. It must be approved by the IRB before any changes are initiated to the research project, unless a change must be made in order to eliminate dangers or hazards to subjects. If the revision is a result of finding new dangers, hazards or changes in risks to subjects, the IRB must be informed as soon as possible. Possible changes could be in areas of:
    - Study design
    - Interventions or procedures
    - Number of subjects
    - Subject population
    - Patient informed consent
    - Patient/Recruitment material
    - Addition or removal of an investigator

The researcher should provide written documentation of the reason for the revision, if it will change the study, how it will affect the risks to the study participant, and what safeguards will be implemented to protect the study participant from the additional risk.

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- Deviations: Investigators are responsible for promptly reporting to the IRB any change or deviation from the protocol. The report should include a description of the deviation or change and the reasons for implementation. If the deviation requires a change in the protocol, then a proposed amendment to the research should be submitted to the IRB and the funding agency for review. Protocol deviations may also be Unanticipated Problems subject to specific IRB reporting timeframes (see below). The deviations are graded according to severity and repeated occurrence and may require action plans to reduce risk.

- Data Safety Monitoring (DSM): All research involving more than minimal risk to subjects must have a Data Safety Monitoring Plan (DSMP) or assigned medical monitors to ensure subject safety during the course of the research. There should be a plan for monitoring subjects' reactions and reporting any anticipated problems or adverse events. Sponsors frequently establish a type of committee or DSM Board for significant risk protocol safety oversight.

- Unanticipated Problems: The Principal Investigator must promptly report all Unanticipated Problems involving risk to subjects or others to the IRB. See Section VI.D.14. for additional information. Unanticipated Problems associated with research subject to UCHealth IRB jurisdiction must be submitted to the UCHealth IRB within 10 days of discovery of the incident, except for adverse events, which must be submitted within 5 days. In addition, adverse events that involve an unforeseen death must be reported within three 3 business days.

- Reporting Non-Compliance: The PI must self-report any serious or continuing noncompliance with the IRB's requirements for protecting human research subjects. This includes any suspension of the research by any agency.

- Record Keeping: All original copies must be secured in a locked filing system for a minimum of 6 years or saved as an e-copy in the e-regulatory system. The following is a list of research-related documents that need to be secured:
  - Progress reports designed to record all observations and data pertinent to the investigation for each subject
  - Research protocol, amendments and updates
  - Signed informed consent documents, or short form with written summary

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- Recruitment materials
- Continuing Review Reports
- Adverse event or Unanticipated Problem reports
- All IRB Correspondence
- All HIPAA research related authorizations and documentation must be kept for a minimum of 6 years.
- All documents must be secured for 3 years following the study completion or discontinuation. OHRP requires documents to be securely retained for 3 years following study completion. FDA imposes a 2-year retention period after the approval of the drug/device or after denial of marketing approval;

- An external monitor or federal audit can happen at any time. When notified of an audit, inspection or site evaluation, the researcher must notify the IRB.

- All reports to and from the FDA and/or Sponsor must be cc'd to the IRB.

- When a physician provides emergency medical care to a subject, involving the test article, without prior UCHealth IRB approval, those activities will not be recognized as research. Collected data may not be used in support of research. "Emergency" and "one-time use" of unapproved drugs and devices requires timely reporting to the FDA, and to the UCHealth IRB, within 5 days.

- Planned emergency medicine research that waives consent must have special IRB approvals before initiation. Contact the IRB for approval requirements.

- Drug Accountability is highly regulated by the FDA. The PI must maintain records for use, dispensing, and disposal of all study drugs, biologics or devices for subjects under their supervision. They must also retain all records required by FDA regulations for a period of two years from the time the application to market the product is approved or for two years after the shipment of product is discontinued.

- Devices: The PI must retain all device accountability records required by the FDA regulations for a period of two years after the investigation is terminated or completed.

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3. Completion of research:

Completion reports should be submitted within 30 days after completion or termination of the study. Completion reports may be submitted in any format that provides adequate information about the status of the study, such as computer printouts, telephone reports, letters, etc. The PI will submit a completed Change in Status Close Out form to the IRB. Completion reports may be submitted by the Investigator's designee at the site.

Honor commitments for compensation to the subjects and provide information about the study results to the research participants. Continue to honor any confidentiality obligations.

REFERENCES:

FDA Guidance Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects October 2009

NIH Frequently Asked Questions Revised September 28, 2011

First Clinical Research Best Practice Glossary

Research Administration Policy Research Conflict of Commitment and Conflict of Interest

University of Colorado Denver Investigator Responsibilities Version 5 April 2, 2015

Drexel University Principal Investigator Guidelines

University of Arizona Handbook for Principal Investigators

Ohio State University Responsibilities of Principal Investigators, Co-Investigators, and Key Personnel Revision Dated August 7, 2012

Dartmouth College Role of the Principal Investigator

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ADDITIONAL REFERENCES

FEDERAL REGULATIONS THAT GOVERN RESEARCH AND ASSURE IRB AUTHORITY

Federal Regulations referred to throughout these policies and procedures are as follows:

- 45 CFR 46 (Title 45 Code of Federal Regulations Part 46: Protection of Human Subjects), referred to as the Common Rule, which applies to research involving human subjects conducted by the Department of Health and Human Services (HHS) or supported in whole or in part by HHS. Available at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm
- 21 CFR 50 (Title 21 Code of Federal Regulations Part 50: Protection of Human Subjects), and 21 CFR 56 (Institutional Review Boards), which apply to all research involving products regulated by the Food and Drug Administration (FDA), including research and marketing permits for drugs, biological products, or mechanical devices for human use, food and color additives, or electronic products. Federal funds do not need to be involved. Available at http://www.fda.gov/oc/gcp/regulations.html
- 45 CFR 160 and 164 (Health Insurance Portability and Accountability Act) which governs the use and disclosure of private health information. Available at http://privacyruleandresearch.nih.gov/
- Good Clinical Practice, US Department of Health and Human Services, Food and Drug Administration, April 1996, *available at* http://www.fda.gov.cder.guidance/index.htm
- 21 CFR 812 (Title 21 Code of Federal Regulations Part 812: Investigational Device Exemptions, which applies to research involving devices used in research involving human subjects. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812

ADDITIONAL SUPPORTIVE MATERIAL REGARDING PRISONER RESEARCH

The following materials are provided to supplement the above procedure.

FDA Prisoner Guidelines

"FDA does not have additional requirements that pertain to research involving prisoners; rather the general requirements for the IRB review and informed consent (21 CFR Parts 56 and 50) apply to such research. However, if the research is conducted or supported by the Department of Health and Human Services (HHS), or conducted in an institution that has assured HHS that it will review all research in accordance with the Common Rule, then the research would be

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subject to 45 CFR 46, including Subpart C, which provides additional protections pertaining to research involving research with prisoners as subjects. Although those additional practices are not required by FDA, they are a good model to follow."

http://www.fda.gov.ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice