

OPERATIONS MANUAL

University of Michigan

Human Research Protection Program

April 2023

HRPP OM Revision Table

Date Updated	Part(s) Updated	Summary of Changes
7/28/2020	Part 1, 2, 5, and 8	Updated references to Flint IRB panel. DIO title was updated. Language referencing FDA Part 11 (Electronic Records) in Part 8 was updated.
10/7/2021	Part 2, 3, 6, 7, 12, 13	References to IRB Council were changed to HRPP Advisory Council in Parts 2, 3, 12 and 13.
1/28/2022	Part 2 and 9	Changes in HRPP organization and leadership were updated in Part 2. Reference to The Office of Technology Transfer (OTT) were updated to Innovation Partnerships in Part 9.
6/9/2022	Part 4	U-M Exemption Category 5 language was updated.
4/13/2023	Part 4 and 8	Clarification about Agency Fund Activities. Updated to describe IRB process for emergency use of investigational article.

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Acronyms/ Definitions

AE	Adverse Events
AAHRPP	Association for the Accreditation of Human Research Protection Programs
AWD	Award Management
Co-I	Co-Investigators
CITI	Collaborative Institutional Training Initiative
COI	Conflict of Interest
COI/COC	Conflict of Interest/Conflict of Commitment
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DOD	Department of Defense
ED	Department of Education
DOE	Department of Energy
DIO	Deputy Institutional Official
EPA	Environmental Protection Agency
eRPM	eResearch Proposal Management
eRRM	eResearch Regulatory Management
FERPA	Family Educational Rights and Privacy Act
FWA	Federalwide Assurance
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FD&C Act	Food, Drug and Cosmetic Act
HIPAA	Health Insurance Portability and Accountability Act
ITS	Information and Technology Services
IO	Institutional Official
IRB	Institutional Review Boards
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
IDS	Investigational Drug Service
IND	Investigational New Drug Application
IRB-HSBS	IRB-Health Sciences and Behavioral Sciences
IRBMED	Medical School Institutional Review Board
MICHR	Michigan Institute for Clinical and Health Research
MICHR MIAP	Michigan Institute for Clinical and Health Research Investigator IND/IDE Assistance
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORCR	Office of Research Compliance Review
ORIO	Other Reportable Information or Occurrences
PI	Principal Investigator
PEERRS	Program for Education and Evaluation in Responsible Research and Scholarship
PAF	Proposal Approval Form
sIRB	Single Institutional Review Board
SOP	Standard Operating Procedure
SPG	Standard Practice Guide
UMOR	U-M Office of Research
UaP	Unanticipated Problem
U-M	University of Michigan
UMRCC	University of Michigan Rogel Cancer Center
VPR	Vice President for Research

PART 1: Introduction, Purpose, and Ethical Principles

Describes the scope of human research conducted at the University of Michigan (U-M), the mission and purpose of the U-M Human Research Protection Program (HRPP), and the authority and ethical principles under which the HRPP operates.

I. MISSION AND PURPOSE OF THE HRPP

The mission of the Human Research Protection Program (HRPP) is to protect the rights and welfare of research participants in research under the U-M oversight. This includes research conducted at the U-M or elsewhere by University faculty, staff, students, trainees, and others when the U-M agrees to review multi-site research. The HRPP's goals are to promote compliance with relevant legal requirements and ethical standards at all levels, while also addressing the needs and concerns of researchers and enhancing support of their endeavors.

The Vice President for Research (VPR), who serves as the Institutional Official (IO) for human research oversight, has established the HRPP as an integrated system consisting of research leadership, administration, and oversight functions. The oversight component includes education and training; quality assurance and compliance; research review units, including institutional review boards (IRBs); and other organizations charged with responsibility for protecting research participants and promoting excellence in all aspects of human research. See Part 4 of this OM for determining what is and what is not human research.

Ensuring success of the HRPP is a joint responsibility. The program is directed by the U-M Office of Research (UMOR), but its implementation requires the active participation and collaboration of many stakeholders including all of the University's executive officers, including the Provost, Chief Financial Officer, Executive Vice President for Medical Affairs, the Chancellors, and leadership of the schools and colleges whose faculty, staff, students, and trainees conduct human research.

II. SCOPE OF HUMAN RESEARCH AT THE UNIVERSITY

A. Types of Human Research Conducted

The U-M supports a broad range of human research including, but not limited to biomedical research and clinical trials, education and behavioral research, research with vulnerable populations, and genomic research.

B. Categories of Participants

Participants in research conducted by the faculty, staff, students, and trainees at the U-M include a diverse group of individuals from the local community, throughout the United States and the world. They reflect the communities in which research is conducted and include individuals who represent different racial, ethnic, and cultural backgrounds and who may speak languages other than English. Some participants are healthy adults, while others are members of specifically identified and protected vulnerable research participant populations (such as children, pregnant women, and prisoners) and other groups of individuals entitled to special safeguards (such as those who are cognitively impaired or economically or educationally disadvantaged).

III.AUTHORITY UNDER WHICH THE HRPP OPERATES

A. Institutional Authority

The Bylaws of the Board of Regents of the University of Michigan assign to the VPR general executive

responsibility for the research programs of the University. As the University's IO, the VPR has established and maintains a federalwide assurance (FWA) between the University and the United States Department of Health and Human Services (HHS), through its Office for Human Research Protections (OHRP). In that assurance, the University pledges to comply with federal regulations for all federally supported research. In addition, the VPR has established and maintains a Department of Defense (DoD) Addendum to the FWA. By signing this addendum, the University agrees to the special terms and conditions for IRB review of projects funded by the DoD.

The IO, on behalf of the University, has established IRBs and grants the IRBs authority to approve, require modifications to secure approval, and disapprove all research activities overseen and conducted by the University. The University has established eight IRBs in two operational offices. They function in coordination with University officials and other review committees but at all times maintain their independence. Individuals who are responsible for University business development are prohibited from serving as members or ex-officio members of the IRBs or carrying out day-to-day operations of the review process.

B. Limitations on Institutional Authority

All human research conducted by the University must be approved by an IRB or granted an exemption as specified in the IRB's standard operating procedures. Research that has been reviewed and approved by a University IRB or external IRB may be subject to further review and disapproval by other review bodies or officials (including the IO); however, no person or organization may override an IRB's disapproval determination.

IV.ETHICAL PRINCIPLES

The VPR has issued Standard Practice Guide (SPG) 303.05. This document establishes the University policy that all human research, regardless of funding source, will be guided by the ethical principles set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled *Ethical Principles and Guidelines for the Protection of Human Subjects Research* (the "Belmont Report") and will comply with applicable University policies and federal, state, and local laws and regulations.

The Belmont principles and their application to human research are summarized below:

Table 1: Ethical principles guiding human research at the University of Michigan. Adapted from OHRP, Institutional Review Board Guidebook (Glossary).

PRINCIPLE	APPLICATION
Respect for Person	Respect for persons requires that protocols (including the informed consent process) be designed to promote personal capacity to consider alternatives, make choices, and act without undue influence or interference from others. The principle is reflected in federal regulations and University policy through requirements that legally effective informed consent be sought and obtained, unless specific requirements for waiver of informed consent are met and appropriately documented; and that subjects with diminished capacity and others who are vulnerable to coercion or undue influence receive special protection or consideration.

PRINCIPLE	APPLICATION
Beneficence	Beneficence entails an obligation to protect individuals from harm. The principle can be expressed in two general rules: (1) do no harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm. It is reflected in federal regulations and University policy through a requirement that principal investigators design and IRBs approve protocols only under circumstances where the benefits to the subjects and the importance of the knowledge to be gained justify the risks to the subjects sufficiently to warrant a decision to allow the subjects to accept those risks.
Justice	Justice requires fairness in distribution of burdens and benefits. The principle is often expressed in terms of treating persons of similar circumstances or characteristics similarly. It is reflected in federal regulations and University policy through requirements that selection of subjects is equitable and is representative of the group(s) that is intended to benefit from the research.

Additional ethical codes and guidelines, including ethical codes of professional societies, may also govern University research.

V. PROTECTION FROM UNDUE INFLUENCE

The University will investigate and resolve any reported attempt to inappropriately pressure (ie to exercise undue influence upon) an IRB or other HRPP unit administrator, member or staff representative because of that individual's role. "Undue influence" refers to interference with the normal functioning and decision-making of an IRB or other HRPP unit, or to influence an IRB or other HRPP faculty or staff member, outside of established processes or through normal and accepted methods, in order to secure a particular determination or outcome. Any attempt to exercise undue influence over the IRB or any other HRPP unit should be reported as follows:

- An IRB or HRPP unit staff or faculty member who experiences undue influence should first report the occurrence to the IRB or unit chair or director, who will attempt to mediate or resolve the concern, in consultation with an IRB or unit chair, the HRPP Director, the Deputy Institutional Official (DIO) or the IO as necessary or appropriate.
- An IRB or HRPP unit chair who experiences undue influence should first report the occurrence to the HRPP Director, who will attempt to mediate or resolve the concern, in consultation with the DIO and/or IO as necessary or appropriate.
- Any individual who believes that undue influence is being exerted by an official in one of the above reporting chains, or who believes that the undue influence has not been appropriately or timely resolved, should report to the next higher level in the reporting chain and ultimately to the Office of the Vice President and General Counsel.
- In addition, individuals who wish to report an incident of undue influence may report through the Compliance Hotline, which allows the reporters to remain anonymous if they choose.

Resolution of incidents involving undue influence depends on the circumstances, but may include disciplinary actions following University standard procedures addressing non-compliance with policy or procedures as described in the Faculty Handbook and OM Part 12.

PART 2: Organization of the HRPP

Describes the organization of the U-M HRPP and the roles and responsibilities of the various units that guide and support the program. This section also describes the general allocation of resources to the various units involved in the HRPP.

I. KEY ORGANIZATIONAL REPRESENTATIVES

An organizational chart identifies key officials and units in the HRPP and illustrates their relationships with one another. The chart displays the incumbent in each role as of the most recent update of this Part of the HRPP Operations Manual (OM).

II. ORGANIZATIONAL ENTITIES THAT SUPPORT THE HRPP

Numerous organizational entities, listed below, contribute to the operation of the University's HRPP. In addition to these entities, other key executive and administrative offices – including the Provost, the Executive Vice President for Medical Affairs, the Chancellors of the Flint and Dearborn campuses, and the General Counsel – all help contribute to the operation of the HRPP. The decentralized organization and shared support system of the HRPP contributes to the program's success by promoting local review and accountability and expert analysis of research proposals and IRB applications. The inherent complexity is managed through a number of mechanisms, including convened standing coordinating committees, overlapping membership on local committees, and informal associations among individuals with HRPP responsibilities.

A. The U-M Office of Research (UMOR)

The mission of UMOR is to catalyze, support, and safeguard U-M research. UMOR promotes the integration of the research, education, and service missions of the University; facilitates the sharing of knowledge and expertise with the larger society; and promotes responsibility in the conduct and administration of these activities. To this end, UMOR establishes the institution's research policies, administers a number of freestanding research units, assists in the creation and incubation of new initiatives, and provides a voice for U-M scholars and scientists in communicating with the public, private industry, and government.

As the University's IO, the VPR sets the tone for an institutional culture of respect for research participants and bears ultimate accountability for the proper conduct of human research at the University. The VPR's primary activities as IO are described further below.

1. Policy Implementation, Communication, and Education

The IO reviews and approves all HRPP policies and represents the HRPP to internal and external stakeholders. In this capacity, the IO:

- Defines the scope of the FWA and obligates the University to comply with its terms;
- Retains authority to make exemption determinations in specific instances or for defined categories of activities and to make categorical determinations of what does or does not constitute human research. See Part 4 of this OM for additional details;
- Makes, or delegates authority to make decisions on IRB reliance agreements, collaborating institution agreements, and individual investigator agreements;
- Is responsible for all budgets within UMOR, including its various administrative and research units; and
- Manages all UMOR units.

The IO promotes communication among research administrators, deans, department chairs, researchers, clinical care staff, research participants, and other stakeholders to maintain a high level of awareness regarding the ethical conduct of research and the safeguard of the rights and welfare of participants. See Part 13 of this OM for additional details.

2. Recordkeeping and Reporting

The IO establishes policies and procedures requiring that IRB records are maintained as required by applicable laws and regulations and that they are accessible to authorized regulators and sponsors. Records for projects that rely on an outside IRB for review and oversight are maintained by the outside IRB in accordance with the U-M IRB Authorization Agreement process.

The IO also establishes policies and procedures on reporting requirements. See Part 6 of this OM for the Principal Investigator's (PIs) reporting responsibilities to the IRBs, University officials, federal regulators, and private sponsors of the PI. See Part 12 of this OM for the written procedures regarding the reporting process for reportable events to the IRB, appropriate institutional officials, the head (or designee) of any federal department or agency conducting or supporting the research, and any applicable regulatory bodies.

3. Monitoring and Oversight

The IO designates IRBs to review research covered by the FWA, as well as other research subject to the HRPP, and delegates additional authority to the IRBs and other units to act on other related issues. In collaboration with other University executive officers, the IO provides sufficient resources, space, and staff to support the IRBs' review, monitoring, and recordkeeping duties.

The IO ensures that appropriate oversight mechanisms are implemented to promote compliance with applicable laws, regulations and IRB determinations. For cooperative research projects that include more than one performance site, the IO ensures that when sharing oversight with another organization, the rights and welfare of research participants are protected, and that when applicable, IRB review arrangements are documented in writing consistent with OHRP guidance. See Part 5 of this OM for additional information on required assurances and registrations and for a discussion on single IRB arrangements when applicable and the University's policy on non U-M researchers participating in U-M projects.

4. Organization

Multiple individuals, units, and functions within UMOR assist in the development, implementation, and enforcement of University policies and procedures for the HRPP.

a. Leadership of the HRPP

The Associate Vice President – Clinical and Human Subjects Research serves as the HRPP Director and, together with the HRPP Associate Directors, advises the IO on all aspects of human research, including policy changes. Reporting to the HRPP Director, the HRPP Associate Directors oversee the HRPP administrative functions, as delegated by the HRPP Director. Responsibilities include:

- Serving as the designated contact person for OHRP under the University's FWA;
- Signing Certificates of Confidentiality on behalf of the University;
- Signing or accepting/approving IRB reliance agreements, collaborating institution agreements, and individual investigator agreements;
- Working with the HRPP Advisory Council to draft institutional policies for effective and efficient administration of the HRPP;
- Coordinating policy implementation initiatives as necessary and appropriate;
- Developing and maintaining the U-M HRPP OM;
- Promoting consistency and addressing identified inconsistencies among various University policies, procedures, and guidance affecting research with participants;

- Facilitating communication and coordination throughout the HRPP;
- Serving as a liaison between the HRPP and individual review units, organizations, and functions, including: the IRBs, the Institutional Biosafety Committee, the Department of Environment, Health & Safety, the Conflict of Interest Review Committees, the Radiation Policy Committee, the General Counsel's Office, campus and health system compliance structures, and academic misconduct investigations and proceedings;
- Assisting with review and reporting of cases involving noncompliance;
- Maintaining the HRPP website; and
- Performing other tasks, as delegated by the IO or the HRPP director.

b. Office of Research and Sponsored Projects

The Office of Research and Sponsored Projects (ORSP) assists faculty and staff members in all aspects of externally sponsored research projects and other scholarly activities, which includes the identification of a potential sponsor, preparation of a proposal, identification and resolution of various administrative, contractual and regulatory compliance issues, negotiation of funding agreements and submission of the documents required to close out the project.

ORSP submits sponsored research proposals to external funding entities, negotiates the terms of those agreements consistent with the mission and goals of the HRPP and law and policy applicable to the University, and arranges for the establishment of appropriate financial accounts when a project is awarded. ORSP obtains and records information about the proposal and project activity, including whether a research proposal involves human research and the status of the IRB approval, through the campus-wide eResearch Proposal Management (eRPM) system that utilizes a proposal approval form (PAF) and award management (AWD) functionality which provides a system level check for appropriate compliance approvals prior to award activation. See Part 10 of this OM for more details on sponsored research.

ORSP project representatives monitor any proposal or award that is flagged for conflict of interest review and will not establish financial accounts without confirmation of review and approval by the appropriate Conflict of Interest Review Committee and by the Board of Regents, (if required). See Part 9 of this OM for additional information on conflicts of interest procedures.

c. Office of Research Compliance Review

The mission of the Office of Research Compliance Review (ORCR) is to monitor the conduct of research, including the protection of participants, by reviewing compliance with the laws, regulations, and University policies. This mission is fulfilled by conducting inspections of allegations and instances of noncompliance; initiating and conducting not-for-cause reviews of research protocols; initiating periodic reviews of HRPP subsystems, including the IRBs; and coordinating the AAHRPP accreditation activities.

d. HRPP Advisory Council

The HRPP Advisory Council advises the IO and DIO with regard to HRPP and IRB policies and procedures. The HRPP Advisory Council includes representation from a broad base of the research community. A current list of members is available on the HRPP website.

The HRPP Advisory Council and its members are encouraged to seek the broadest possible input from the U-M research community and bring those perspectives to the deliberations of the Council. The Council will focus on specific topics and question areas of interest and importance to the HRPP. Specific functions of the HRPP Advisory Council include:

- Providing feedback from the U-M research community to the HRPP;
- Providing input on development and implementation of new policies, processes, or initiatives;
- Reviewing OM policies, procedures, or guidance emerging from the eResearch process and elsewhere, and recommending specific revisions or recommending adoption thereof;
- Advising on the procedures developed by the various IRBs for developing and updating local policy;
- Reviewing the adequacy of existing training and quality assurance functions and recommending improvements;
- Creating a communication and feedback loop to drive process improvement; and
- Performing other tasks as requested by the chair or the IO.

The IO generally will solicit HRPP Advisory Council input but may develop and implement institutional policies and approve IRB and other review unit SOPs prior to Council review or recommendation, in order to ensure the efficient operation of the HRPP.

e. eResearch

To support the management of research information at the University, UMOR and Information and Technology Services (ITS) Enterprise Application Services maintain an electronic administrative system called *eResearch*. eResearch supports efforts of faculty, staff, and students to comply with federal, state, and University requirements aimed at ensuring the safety and privacy of persons who volunteer to participate in research studies. eResearch also supports the administrative functions involved with conflict of interest management, grants, and sponsored projects. Regular updates are made to eResearch with input from the HRPP Advisory Council, and administrative and academic units that support the HRPP. Requested changes are prioritized and approved via eResearch governing committees. Final authority to implement changes belongs to the Assistant Vice President for Research — Regulatory and Compliance Oversight and is delegated to the ITS Assistant Director for eResearch Administration Systems.

f. Research Associate Deans

The Research Associate Deans (RADs) of the schools and colleges generally gather monthly at meetings convened by the Associate Vice Presidents for Research. The meetings facilitate communication between central administration and faculty through their RADs as well as providing a forum for RADs to share initiatives and experiences in the development, conduct, and administration of research in their own units. The HRPP Director informs the HRPP Advisory Council of any issues and concerns related to the operation of any component of the HRPP that are brought forward by the RADs. The RADs also review and provide feedback concerning policy and procedure initiatives.

B. The Academic Units

The University's schools, colleges, departments, and other academic units whose appointed faculty and staff conduct research with participants are responsible for ensuring that sufficient resources (including facilities and equipment, personnel, regulatory support, and other financial and non-financial support) are allocated to sponsored and non-sponsored research activities to protect participants engaging in those activities. For sponsored activities, the academic units certify compliance with this requirement through eRPM.

In addition, the academic units are permitted and encouraged to develop, implement, and enforce local policies and procedures governing University research, so long as those policies are consistent with the requirements of this OM and applicable University policies. Academic unit policies and procedures may address issues such as the following:

- Mentoring programs for new faculty and continuing education for experienced faculty, to ensure familiarity with best research practices and with applicable regulatory and institutional requirements;
- Administrative requirements designed to ensure that limited financial, facility, staff, and participant resources are appropriately allocated to individual projects or groups of projects; and
- Substantive peer review requirements designed to promote sound research design and scientific integrity in any University research.

All sponsored projects must be approved both at the local academic unit level and through ORSP and this is accomplished through eResearch. In addition, through eResearch, the academic units may require that any individual projects or categories of projects, regardless of sponsorship, be approved at the unit level before they are initiated. IRBs may withhold approvals pending confirmation of approval or receipt of additional information (or both) from the academic unit and from other review units at the University or at other performance sites.

C. The Institutional Review Boards (IRBs)

Each of the University's IRBs sits within an administrative structure that provides the resources for and oversees the general operation of the IRB. The Medical School provides resources and administrative support for IRBMED. UMOR, UM-Flint and UM-Dearborn provide resources and administrative support for the IRB Health Sciences and Behavioral Sciences.

The business functions of the administrative units are separated from the ethics review function. The administrators of the units supporting each IRB are not involved in the day-to-day operations of the IRB review process.

1. Authority of the University of Michigan Institutional Review Boards

Except for research that is specifically exempted in accordance with applicable laws and regulations and Part 4 of this OM, the University's IRBs review and monitor all University research involving participants, regardless of funding source, as well as research with participants as delineated by IRB reliance agreements. In addition, the specific types of research with participants that must also be reviewed and approved by other departments, divisions or units of the University are described in section D below. Depending on the nature and scope of a project, a University IRB may withhold its approval pending confirmation of approval by, or receipt of additional information from, any of these units or from review units at other performance sites. Further, the University IRBs have the right to observe or have a third party observe the consent process and the conduct of research.

Each University IRB also has the authority to suspend or terminate approval of research that is not being conducted in accord with the IRB's requirements or that has been associated with unexpected serious harm to participants or others. Any suspension or termination of approval must be imposed in compliance with the IRB's SOPs and, at a minimum, include a statement of the reasons for the IRB's action. Promptly following any such suspension or termination, the IRB must report its action to the IO or DIO, or their designee, who then follows the procedures outlined in Part 12, Section III of this OM.

2. Primary Responsibility to Human Participants

Each IRB's first and most important function is to protect the rights and welfare of human research participants. The safeguarding of participant rights and welfare must at all times take precedence over the goals and requirements of any research endeavor overseen by the IRB. IRB members and staff, as well as

researchers submitting applications to the IRB, all must be informed of and understand this obligation.

3. Standard Operating Policies, Procedures and Guidance

Each of the University's IRBs has developed and documented its own SOPs, together with related guidance, that are consistent with the requirements of Part 3 of this OM. Having separate IRBs allows each to tailor its activities to the specific types of research it oversees, to the ethical issues raised by that research, and to the local context. Separate and specific IRBs also facilitate more targeted and effective education and training for IRB members and staff and for the researchers and others who interact with the IRB.

The administrative units overseeing the operations of the IRBs are responsible for the development, maintenance, review, and updating of IRB-specific SOPs. IRB SOPs and any substantive amendments may be implemented only upon the approval of the IO or designee.

D. Other Research Review and Support Units

1. Michigan Institute for Clinical and Health Research

The Michigan Institute for Clinical and Health Research (MICHR) is an institution-wide institute aimed at providing education, resources, infrastructure, consultation, and guidance in the development and conduct of clinical and translational research at the University of Michigan. MICHR is the recipient of the NIH-funded Clinical and Translational Sciences Award (CTSA).

2. Clinical Trials Support Office (CTSO)

The Clinical Trials Support Office (CTSO) is part of the Medical School Office of Research and serves as the hub for the seven trans-departmental Clinical Trials Support Units (CTSUs). All clinical trials at Michigan Medicine are required to be supported by a CTSU.

3. Rogel Cancer Center

a. Oncology Clinical Trials Support Unit (O-CTSU)

The Oncology Clinical Trials Support Unit (O-CTSU) serves as the centralized core facility of all clinical research trials conducted by researchers at the University of Michigan Rogel Cancer Center (UMRCC). The O-CTSU offers a broad range of support services including regulatory and data management services.

b. Protocol Review Committee

The Protocol Review Committee (PRC) is a multidisciplinary committee that provides peer review of the scientific merit, prioritization, and progress of all cancer clinical trial studies.

c. Tissue Procurement Service

The Tissue Procurement Service ensures that relevant ethical and administrative guidelines are followed in the procurement and distribution of human tissue for research purposes.

4. Conflict of Interest Committees

The UMOR Conflict of Interest Committee reviews potential conflicts of interest in research outside of the Medical School.

The UMMS Conflict of Interest Review Board addresses potential conflicts of interest in research performed by Medical School faculty, staff, and trainees, and their affiliated co-investigators in other schools and colleges as appropriate.

The Institutional Conflict of Interest Committee reviews potential conflicts of interest in research involving financial interests of the University (eg investments held by the University in a company) or an executive officer, dean, or an institute or center director with day-to-day responsibility for the supervision of faculty and staff participating in research conducted at or under the auspices of the University.

5. UMHS Clinical Engineering

Michigan Medicine Clinical Engineering is responsible for the technical and engineering support of most of the medical equipment at Michigan Medicine, with certain exceptions for specialized services.

6. Institutional Biosafety Committee

The Institutional Biosafety Committee (IBC) oversees all recombinant DNA and synthetic nucleic acid molecule research at the University of Michigan, including human gene transfer clinical trials. The IBC also oversees research with other potentially hazardous biological agents including infectious agents (eg viruses, bacteria), biological toxins, human-derived materials, and certain animal-derived materials. The BSL3 subcommittee of the IBC reviews research with select agents and toxins regulated by HHS and the U.S. Department of Agriculture (USDA), and serves as the Institutional Review Entity required for identification and review of life sciences Dual Use Research of Concern (DURC).

7. Michigan Medicine Research Pharmacy

All investigational drug protocols conducted by Medical School faculty or using Michigan Medicine facilities must be reviewed by the Michigan Medicine Research Pharmacy prior to submission to the IRBMED. The Research Pharmacy is responsible for: (i) assuring appropriate storage and handling of all investigational drugs; (ii) assuring inventory accountability of all investigational drugs; (iii) serving as a central source of information for all investigational drugs used for humans; (iv) dispensing medications only for protocols that have approval of the IRBMED and only in a manner consistent with the requirements of those protocols; and (v) distributing appropriate information about investigational drugs and their use in particular study protocols to individuals with direct care responsibilities for patients enrolled in those studies.

8. Radiation Safety Service

The Radiation Safety Service (RSS) oversees the use of radioactive materials and radiation-producing devices at the University, and promotes radiological safety through safety training, professional guidance, and technical support, in accordance with federal and state regulations and the University's Byproduct Material License.

9. Research Centers

A number of other centers distribute resources or provide other support on a merit basis, or perform functions such as peer review and research oversight, which include, but are not limited to, UMOR, the Alzheimer's Disease Center, the Institute for Research on Women and Gender, and the Michigan Diabetes Research and Training Center.

10. Additional Units Supporting the HRPP

A variety of additional administrative units and functions contribute to the operation of the University's HRPP. Examples include:

- Biomedical Research Council
- Research Administrators' Network
- Center for Statistical Consultation and Research
- Michigan Medicine Corporate Compliance
- UMMS Office of Research
- IRBMED Leadership

E. Independence of Research Review Units and Response to Undue Influence

Although the research review units, and in particular the IRBs, are accountable to the IO for appropriate conduct of research and for protecting research participants they maintain their independence by formulating their own policies and procedures and, in some cases, through independent funding and oversight mechanisms. Specific procedures for reporting and responding to allegations of noncompliance, including exercise of undue influence, are described in Part 1 and Part 12 of this OM. In addition, all faculty, staff, and trainees have access to advice and assistance outside of their units and traditional lines of supervision through the Provost's Office, the Office of the Vice President and General Counsel, and other central University offices.

F. Resources

The University maintains adequate resources for support of the operations of the HRPP, including but not limited to resources such as space and personnel, in order to meet accreditation standards. Resources for the HRPP components are provided through the annual budget review processes in the administrative units in which the components reside. The need for study-specific resources is evaluated at the local level. Researchers and sponsoring units are responsible for ensuring that sufficient resources are allocated to all projects, whether sponsored or investigator-initiated. See Part 3 of this OM for details on study-specific resources required for IRB approval.

The need for incremental or off-cycle resources may emerge as a result of special or unusual demands on the offices, either as reported by the offices or by quality assurance/review activities, or by Executive Officer deliberations. Requests for incremental or off-cycle resources may be made to the responsible unit at any time, or to the IO, or through the IO to the Provost.

PART 3: HRPP Policy

Describes the process by which HRPP policies are developed, approved and implemented, and articulates minimum requirements for IRB standard operating policies and procedures.

I. INTRODUCTION

Rulemaking within the U-M is divided three ways: (i) the Bylaws of the Board of Regents; (ii) Regents Policies; and (iii) rules adopted by subordinate University authorities, under delegated legislative powers, that become effective as provided by such subordinate authorities. HRPP policies fall within the third class of rulemaking.

II. HRPP OPERATIONS MANUAL

The HRPP OM is the primary location for compiling, organizing, integrating, and pointing to the rules, policies, practices, and guidance encompassing the University's HRPP. The IO has approved the OM and approves each substantial modification or amendment to it. Records of such approval are maintained in the UMOR.

At least once every five years, typically in conjunction with the Association for the Accreditation of Human Research Protection Programs (AAHRPP) re-accreditation cycle, UMOR initiates a comprehensive review of the OM. Revisions may be made at any time, however, as required by changes in law, ethical standards, institutional policy, quality assurance activities, or other considerations. Non-substantive revisions (eg to correct typographical errors, update links or incorporate summaries of new or revised laws or regulations governing the HRPP) may be made upon approval of the HRPP Advisory Council and communicated to the IO or delegee by the HRPP Director.

III. IRB STANDARD OPERATING POLICIES AND PROCEDURES

Each IRB designated by the University to review and monitor human research under the University's Federalwide Assurance (FWA) must adopt SOPs. The IRBs may issue additional guidance as necessary to ensure appropriate review and oversight of University research and to facilitate compliance by researchers and research staff with applicable laws and regulations and with University policy, including IRB requirements.

The SOPs must be consistent with this OM, other central institutional policies (eg SPGs), and applicable laws and regulations. IRBs are free, however, to implement and enforce additional or more restrictive policies and procedures. SOPs may incorporate, by reference, elements of this OM, as appropriate. SOPs, however, are intended to be stand-alone descriptions of the actual procedures used by the IRB.

SOP Development, Review, Update, and Maintenance

The SOPs must describe the development, review, update, and maintenance processes, including the following activities:

- Responding to requests from the HRPP for new local policy development;
- Considering input from IRB chairs, members, and staff, as well as researchers and other stakeholders;
- Soliciting and considering input from standing and *ad hoc* research and advisory councils;
- Reviewing SOPs at regular intervals, generally in conjunction with accreditation activities or revision of this OM; and
- Revising in response to comments by the HRPP Advisory Council and the IO or designee.

When writing SOPs, IRBs should review Sections A through E, below, and include all applicable provisions.

SOP Approval Process

All IRB SOPs, including substantive revisions, must be reviewed and approved prior to implementation as outlined in that IRB's SOPs and according to the procedures of the office providing resources and administrative oversight of that IRB, as well as the HRPP Director.

The HRPP Director need not wait to approve revised SOPs in their entirety but instead may, at the request of the IRB and at his/her discretion, review and approve for implementation individual components as they are developed. IRBs may issue additional guidance without prior approval, but guidance must be revised or rescinded if directed by the HRPP Director. Guidance may require additional approvals at the unit level.

A. IRB Authority and Guiding Principles

SOPs must describe:

- The authority under which the IRB is established;
- The relationship of the IRB to the IO and other institutional leadership;
- The scope of its jurisdiction over human research conducted at the U-M or by its faculty, staff or trainees;
- The ethical principles under which it operates; and
- The IRB's purpose (ie to protect research participants).

IRBs, as a matter of policy, may regularly apply ethical principles in addition to those described in the Belmont Report (eg the Nuremberg Code), or comply with laws, regulations, or policies other than those described in this OM (eg guidelines published by the International Council on Harmonisation). However, IRB SOPs must describe additional guiding principles in sufficient detail to apprise researchers of the standards against which their studies will be reviewed and monitored, including sponsor specific requirements. This requirement does not apply to the concerns and considerations that an individual reviewer may bring to his or her analysis of an application nor preclude the IRB from considering any principles or rules beyond those formally articulated in its SOPs on an *ad hoc* basis.

B. IRB Organization and Personnel

SOPs must describe the following:

- How the composition of the IRB is periodically evaluated and, when necessary, adjusted so that the membership and composition of the IRB meet legal, regulatory, and organizational requirements;
- The selection, appointment, length of service, duties, attendance requirements, training, and evaluation of IRB chairs and vice chairs, members and alternate members;
- The duties and functions of IRB staff and their relationship with IRB chairs and vice chairs, members, researchers, and other stakeholders; and
- Any ethical expectations of these individuals in addition to those described in this OM.

1. IRB Composition

Each IRB must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly subject to that IRB's oversight. SOPs must provide that:

a. The IRB will be sufficiently qualified through the experience and expertise of its members, and their diversity (including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes), to provide for effective review of research.

b. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to determine the acceptability of proposed research in terms of institutional commitments and policies, applicable laws and regulations, and standards of professional conduct and practice. To this end, the SOPs will require the IRB to include members knowledgeable in these areas.

c. For any IRB that regularly reviews research that involves vulnerable participants, such as children, prisoners, persons who are cognitively impaired or lack decision-making capacity, or persons who are economically or educationally disadvantaged, consideration must be given to inclusion as members on the IRB of one or more individuals knowledgeable about and experienced in working with such participants.

d. When reviewing U.S. Food and Drug Administration (FDA) regulated studies, the IRB must include at least one physician.

e. The IRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. The IRB also must have members with sufficient knowledge of the specific scientific discipline(s) relevant to the research that it reviews.

1) A scientist is a member whose training, background, and occupation would incline him or her to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline.
2) A nonscientist is a member whose training, background, and occupation would incline him or her to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline.

f. The IRB must include at least one member who is not otherwise affiliated with (or an immediate family member of a person affiliated with) the University. The University supports the efforts of the IRBs to include additional unaffiliated members.

1) "Unaffiliated" individuals include:
    - University patients or research participants or former students of the University who have no other affiliation with the University are not considered affiliated
    - Payments to unaffiliated members at reasonable market rates for their services to an IRB do not render them affiliated.

2) "Affiliated" individuals include:
    - Full-time employees
    - Part-time employees
    - Current students
    - Members of any governing panel or board of the University
    - Healthcare providers with medical staff membership or other credentials to practice at University clinical sites
    - Volunteers working at the University on business unrelated to the IRB

IRB rosters reflect the above requirements and are maintained by the IRB offices. The IRB offices submit updated rosters to UMOR. UMOR registers each IRB with OHRP and updates registrations as needed.

2. Use of IRB Consultants

The IRB must possess sufficient knowledge of the local research context to fulfill its review responsibilities under federal regulations and this OM. To supplement this knowledge, the IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB.

SOPs must include provisions that:

- Describe when and how an IRB will use consultants to supplement the IRB's knowledge;
- Prohibit these consultants from voting with the IRB; and
- Require consultants to disclose any relevant conflicts of interest or commitment before agreeing to assist in a review.

3. Alternate IRB Members

SOPs may include provisions for designating alternate members to an IRB. If they do, each alternate IRB member should have experience, expertise, background, professional competence and knowledge comparable to that of the primary IRB member whom the alternate would replace. SOPs must describe the function of alternate members and procedures regarding:

- Determining whether the primary member or his/her alternate is the official voting member of the IRB for review of protocols or applications (or any individual protocol or application); and
- Ensuring that only the vote of one is counted in any particular circumstance.

4. IRB Educational and Training Activities

SOPs or other documents must describe:

- Any orientation procedures for new IRB chairs and vice chairs, members and alternate members, and staff;
- Continuing education requirements and opportunities for IRB chairs and vice chairs, members and alternate members, and staff;
- Available reference materials (eg library resources, internet sites, etc.); and
- Training and education requirements for researchers who plan to submit IRB applications and reports.

5. IRB Compensation and Liability Coverage

The SOPs or other policies or guidance developed by the administrative unit responsible for the IRB's operations must describe arrangements, if any, for compensating IRB chairs and vice chairs members and alternate members, and consultants for their IRB service. Liability coverage is a matter of institutional policy and is described in risk management policies. In brief, the University's self-insurance policies generally cover the actions of faculty, staff, trainees, and non-affiliated volunteers performing authorized activities on behalf of the University (such as membership on an IRB). These policies do not cover acts of willful misconduct or illegal activities, nor do they cover losses for personal property or for personal injury of non-employees sustained while engaged in the authorized activities.

6. Evaluations of IRB Chairs, Members, Staff, and Regular Consultants

The performance of each IRB chair, vice chair, member, staff, and regular consultant must be evaluated regularly. SOPs must:

- Describe the process and content that is used to conduct evaluations of IRB chairs, vice chairs, members, staff, and regular consultants;
- Indicate the frequency of the evaluations;

- Identify who conducts the evaluations; and
- Describe how the results of the evaluation are used.

7. IRB Member and Consultant Conflicts of Interest
SOPs must include:

- A statement that no IRB member or consultant may participate in any review of any project in which the member has a conflicting interest (as defined in Part 9 of this OM), except to provide information requested by the IRB;
- A statement that any conflicted IRB member or consultant may not be present for, nor count for quorum, nor participate in the deliberations of, nor vote on the disposition of an application in which the member has a conflict. However, the member may be invited by the IRB to provide information relevant to the IRB's consideration of the application;
- A description of the process used by IRB members and consultants to report conflicts of interest and commitment with any IRB application for review; and
- A description of the process the IRB will use to manage reported conflicts.

Part 9 of this OM provides further information on IRB member and consultant conflicts of interest.

C. IRB Review Policies and Procedures

SOPs must describe key IRB review policies and procedures in sufficient detail to inform IRB members and staff, researchers, and other stakeholders of the IRB's rules and expectations. Policies and procedures must include, at a minimum, the elements described below in Subsections 1 to 7. To the extent these elements are addressed through this OM or other institution-wide policy, they need only be referenced in the IRB SOPs.

1. IRB Jurisdiction and Authority
SOPs must describe:

- What types of studies are typically reviewed by the IRB;
- The authority of the IRB to approve, disapprove or require modifications for approval of human research under its jurisdiction;
- The IRB's authority to suspend or terminate approval of a study, or to place restrictions on the performance of the study, and the circumstances under which these actions may be taken; and
- If the IRB issues a "not regulated" determination or notifies the researcher that research is exempt from review, the procedures that researchers must follow to request such determinations and the internal processes to perform them.

2. Institutional Approval/Disapproval of IRB Decisions
SOPs must acknowledge that:

- Research approved by an IRB is subject to disapproval by the IO and, as applicable, other institutional officials;
- No institutional official, including the IO and the University President, is empowered to overrule an IRB's disapproval.

3. Submission of IRB Applications and Reports
The University has developed a web-based system for submission, routing, approval, and management of human research information. The system, called eResearch Regulatory Management (eRRM), is designed to help the University meet its obligation to conduct research in an ethical manner and in accord with laws and

regulations governing research conduct. Access to eResearch is granted based on roles and oversight responsibilities. eRRM is designed so that:

- Only one PI is allowed for each application;
- The PI must assume full responsibility for a project and for compliance with applicable laws and regulations and institutional policy and must be knowledgeable about a project's existence, scope, and progress;
- The PI is required to execute the final command to submit a report or application to ensure that the PI has reviewed the entire content of the submission and has approved all information submitted, including all supporting documentation (and in doing so to make certain attestations regarding the conduct of the project and his/her involvement in it and certify that the PI is responsible for that information);
- The PI may specifically delegate the responsibility to a Co-Investigator or the faculty mentor to submit reports of an Adverse Event (AE) or Other Reportable Information or Occurrence (ORIO) due to the possible time-sensitive nature of these reports, although the PI is still ultimately responsible for these reports; and
- Exceptions to this policy are limited and must be approved by the IO or designee

SOPs must describe the PI role and responsibilities for submission of applications and reported to the IRB and the process to be used.

4. General Review and Approval Procedures

The SOPs must describe the procedures the IRB follows when making the determinations specified in Subsections (a) to (f) below.

a. Determining Whether and Under What Authority the Research is Regulated

The SOPs must describe the role of IRB staff in determining whether the research is regulated by the IRB. In making this determination, the IRB considers the following with respect to each application submitted to the IRB for initial, amendment, or continuing review:

- Is the activity described in the application human research as defined in the Common Rule?
- Is the activity human research as defined in FDA regulations?
- Is the University of Michigan engaged?
- Does the research qualify for exemption from IRB oversight?

These determinations are made consistent with the guidance provided at the U.S. Department of Health and Human Services Human Subject Regulations Decision Charts and in consultation with IRB administrators or chairs, as appropriate. If the research:

- Involves **activities or data subject to other rules or regulations,** such as the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, the Health Information Technology for Economic and Clinical Health Act (HITECH) Security Rule, the Family Educational Rights and Privacy Act (FERPA) or rules of other federal agencies, the SOPs describe the process for reviewing and ensuring compliance with these other regulations or rules.
- Is **not regulated**, the SOPs indicate that a PI may obtain documentation of a "not regulated" determination for IRB applications submitted through eResearch either via review by an IRB staff member to confirm the not regulated status or via a system-generated determination issued through the smart form logic of the IRB application.
- Is **exempt**, the SOPs direct an IRB staff member to ensure that the application indicates an appropriate request for an exemption determination, or to direct the PI to revise the application to do so, and, to ensure that, where appropriate, the IRB conducts a "limited IRB review." In addition, the

SOPs allow for a system-generated exemption determination through the smart form logic of the IRB application for certain types of exempt research.

b. Reviewing IRB Applications

1) Information Required for IRB Review

IRBs must obtain sufficient information prior to review of applications for initial review, continuing review, and review of amendments to previously approved research, so that it can apply and satisfy the requirements for approval of research. SOPs must describe what information the IRB must obtain prior to review of an application.

2) Review Process/Primary Reviewers

SOPs must describe the IRB's review and approval process, including any primary reviewer process used for initial review, continuing review (see OHRP's Guidance on Continuing Review), review of protocol changes, review of reports of unanticipated problems involving risks to participants or others, or of noncompliance, particularly serious and/or continuing noncompliance. SOPs must include all of the following:

a. A list or description of specific documents and other information distributed or otherwise communicated to primary reviewers (if applicable), and to all other IRB members for each review;
b. The timing of the distribution;
c. Links to all supporting awards, contracts, and other sponsor information
d. The regulatory criteria considered by the IRB and primary reviewers (if applicable); and
e. The range of possible actions taken by the IRB for protocols undergoing initial or continuing review and protocol changes undergoing review.

3) Approval with Conditions

If the IRB approves research with conditions (approved pending contingencies), SOPs must describe the following:

a. A study may not be approved with conditions if substantive changes or requirements, requests for more information or documentation, or clarification of other issues are necessary in order for the IRB to determine that the criteria for IRB approval are met.
b. Minor changes or requirements may be reviewed for approval by a staff member or IRB member designated by the IRB Chair, or by the IRB Chair.

c. Determining Frequency of Review

SOPs must describe how IRBs determine the frequency of review of each study, including:

1) IRBs review all non-exempt University research at least once each year, except for:

a. Minimal risk research that does not require continuing review in accordance with applicable regulatory, University, or sponsor requirements.
b. Non-FDA regulated research that has progressed to the point that it involves only one or both of the following:
    i. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

ii. Accessing follow-up clinical data from procedures that participants would undergo as part of clinical care.

2) To ensure proper monitoring of studies, the IRB may determine that some projects require review more often than annually. SOPs should include the criteria the IRB uses to make these determinations. For example, an IRB may set a shorter approval period for high-risk protocols or protocols with a high risk-to-potential benefit ratio.

3) For projects that require a continuing review, a statement that the expiration date is the last date the protocol is approved, and the method of calculating the expiration date. Effective dates of IRB approval and expiration are noted in the approval letters for initial review, continuing review, and amendments. The eRRM uses the expiration date to calculate the end of the approval and the exact time at which the approval period ends is noted on the approval letter by the following statement: "Approval for this study expires on 11:59 p.m. on xx/xx/xxxx."

4) For non-FDA regulated projects qualifying for expedited review, continuing review is not required unless the reviewer determines that it is necessary or is required by other law or regulation. The effective date of approval is cited in the approval letter for initial review and includes a notice that continuing review is not required.

d. Monitoring and Verification

SOPs must describe how the IRB determines which projects need enhanced monitoring, such as verification from sources other than the researchers that no material changes have occurred since previous IRB review. SOPs should include specific criteria used to make these determinations, for example:

- Random selection of projects;
- Complex projects involving unusual levels or types of risk to participants;
- Projects conducted by researchers who previously have failed to comply with applicable regulations, institutional, or IRB requirements;
- Projects where other concerns have been raised about possible material changes occurring without IRB approval.

e. Reporting Changes in Research to the IRB

SOPs must describe the process for submitting and approving changes to research projects, including all of the following:

1) The eResearch IRB application is the method by which researchers report and IRBs approve changes in non-exempt research.

2) The IRB requires prompt submission of proposed changes in research activity via an amendment prior to initiation of the change.

3) Changes may not be initiated until approved by the IRB except when necessary to eliminate apparent immediate hazards to the participant. Changes initiated without IRB approval in order to eliminate apparent immediate hazards to the participant:

   a. Are promptly reported to the IRB.
   b. Are reviewed by the IRB to determine whether each change was consistent with ensuring participants' continued welfare.

4) In approving such changes, the IRB will apply applicable regulatory criteria and will require that any significant new findings that might relate to willingness to continue participation are provided to participants; and

5) The HRPP ensures compliance with this requirement through its post-approval monitoring program and the IRB's internal monitoring activities.

f. Lapses in IRB Approval

For projects requiring continuing review, SOPs must describe the process used to prevent lapses of IRB approval of a study due to late submission of a required continuing review application, including all of the following:

1) The IRB requires researchers to submit a continuing review application before expiration of IRB approval, and in ample time for IRB review.

2) To assist the researchers in meeting this requirement, eResearch provides notification of impending expiration and directions for submitting a continuing review application.

If a researcher fails to provide a continuing review application to the IRB, and the IRB has not completed the review and approval of the application by the expiration date of the current approval, the study will be considered lapsed and:

1) All research activities must stop;

2) Interventions and interactions on current participants must stop, unless the IRB finds it is in the best interest of individual participants currently participating in the study to continue the research interventions or interactions;

3) Enrollment of new participants during a lapse is prohibited;

4) The IRB will remind researchers that resources must not be expended for unallowable activities; and

5) The IRBs notify other University units of lapses, as needed.

5. Expedited Review

SOPs must describe the expedited review process, including:

- Which categories of projects or applications may be eligible for expedited review;
- The process (if any) for requesting expedited review;
- The procedures for reviewing applications by expedited review;
- The rationale for requiring continuing review of research qualifying for expedited review;
- Review of amendments using the expedited procedure; and
- The method for keeping all IRB members apprised of applications that have been approved on an expedited basis.

a. Applicability Criteria and Categories

SOPs must describe the types of research that are eligible for expedited review as specified by OHRP's Expedited Review Categories, FDA and list of expedited review categories. An IRB generally may use

expedited procedures (through its chair or one or more experienced members designated by the chair) to review research meeting the following criteria:

1) Research procedures present no more than minimal risk to participants;

2) The identification of the participants and/or their responses will not reasonably place them at risk of criminal or civil liability or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal;

3) The research is not classified; and

4) The research falls into one or more of the categories of projects or applications appearing on a list of studies that may be reviewed by the IRB through an expedited review procedure published by the Secretary of the Department of Health and Human Services, and only in those categories. (See 45 CFR 46.110 and 21 CFR 56.110).

The IRBs may also use the expedited review procedure for research for which limited IRB review is a condition of exemption under 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8). Note: U-M has not implemented broad consent for storage, maintenance, and secondary research with identifiable private information or identifiable biospecimens and therefore regulatory requirements regarding exempt research in 46.104(d)(7) and (8) are not applicable.

b. Minor Changes

The IRB also may use expedited procedures to review "minor" changes to research previously approved by the full committee. SOPs must provide that a proposed change in research is deemed “minor” if it does not significantly affect an assessment of the risks and benefits of the study and does not substantially change the aims or design of the study. A modification cannot be deemed "minor" if it involves the addition of procedures that involve more than minimal risk or that do not fall into categories (1) - (7) of research published by the Secretary of the HHS.

Examples of "minor" changes to a research study include, but are not limited to, the following:

1) Addition or deletion of study team members;

2) Addition of procedures that do not significantly increase risk to participants, considering the original purpose and study design of the approved study (ie new procedures that fall under any of the expedited categories can usually qualify as minimal risk);

3) Removal of research procedures that would thereby reduce the risk to no more than minimal (ie procedures now meet expedited research categories);

4) Addition of non-sensitive questions to a survey or interview, and procedures;

5) Addition of, or revision to, recruitment materials or strategies; and

6) Change to improve the clarity of statements or to correct typographical errors provided that such changes do not alter the content or intent of the statement.

The University may also undertake demonstration projects that allow for the addition of expedited review categories for research that is not federally sponsored.

c. Expedited Reviewers

SOPs must describe how expedited reviewers are chosen. Generally, IRB Chairs appoint experienced IRB members to serve as expediting reviewers. For purposes of this policy, a member is deemed experienced if he or she has completed all mandatory education for IRB members, has served on the IRB for a minimum of six months or has described and documented comparable experience, and been approved by the IRB Chairs as qualified to perform expedited reviews. The IRBs may adopt more restrictive criteria in their SOPs.

d. Expedited Review Determinations

If the IRB employs expedited review procedures, the SOPs should address the method the IRB will use to ensure that expedited reviewers either approve or forward the application for full board review within a reasonable period of time. The expedited reviewer must review the same materials that the convened IRBs receive for protocols reviewed by the convened IRB. Applications may not be disapproved using expedited procedures; rather, full board action is required for disapproval.

e. Requirements for Continuing Review

Continuing review for projects qualifying for expedited review is not required for non-FDA regulated research, unless otherwise required by law or regulation. Expedited reviewers must provide documented rationale for requiring continuing review. If a reviewer determines that continuing review is required, IRB SOPs must describe the process whereby at least one IRB member reviews the complete protocol, including a status report (continuing review application) and any amendments previously approved by the IRB.

IRB SOPs must describe an alternate process to maintain oversight of ongoing research for projects approved using the expedited procedure and no longer requiring continuing review.

f. Limitations on Use of Expedited Review

SOPs must describe any limitations placed on the use of expedited review, including:

1) The IRB Chair may use their discretion to refer studies qualifying for expedited review to the full committee;

2) For federally supported or FDA-regulated research, the relevant department or agency head may restrict, suspend, terminate or choose not to authorize an institution's or IRB's use of expedited review procedures; and

3) The IO retains authority to require full-board review of any project or category of projects.

6. Criteria for IRB Approval

IRBs ensure research submitted for initial review, continuing review, and review of modifications, whether reviewed by the convened board or by expedited review procedures, is approved only when all of the requirements in 45 CFR 46.111 and Subparts B, C, and D, as applicable and/or 21 CFR 56.111 and Subpart C, as applicable are met. SOPs must include all of the criteria described below.

a. Scientific Merit and Feasibility

In its review of research applications, the IRB considers whether research procedures are consistent with sound research design in order to yield the expected knowledge and examines the scientific merit in relationship to the risks and benefits of the research.

b. Minimizing Risk

A research plan approved by the IRB must ensure that risks to participants are minimized by using procedures consistent with a sound research design that do not unnecessarily expose participants to risk, and whenever appropriate, by using procedures already being performed on participants for clinical purposes. When ensuring that risk is minimized, the IRB should evaluate the resources available at each site where research will be conducted (see (j) Resources).

c. Risk-Benefit Analysis

Research may be approved only if the risks to participants are reasonable in relation to any anticipated benefits to participants and to the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that participants 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 (eg the possible effects of the research on public policy) as among those research risks or benefits that fall within the purview of its responsibility.

d. Equitable Participant Selection

An IRB must determine that recruitment and enrollment plans will promote equitable participant selection. In making this assessment, the IRB should review any proposed direct advertising to prospective participants (ie communications intended to be seen or heard by potential participants to solicit their participation in a study). The IRB should also take into account the purposes of the research, the setting in which the research will be conducted, the influence of payments to participants, and participant selection criteria. The IRB should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, persons who are cognitively impaired or lack decision-making capacity, or economically or educationally disadvantaged persons.

e. Informed Consent and Parental Permission

1) General Requirements

Information given to participants as part of informed consent must meet applicable regulatory and institutional requirements, including those described in Part 6 of this OM. Generally, all of the elements of informed consent and documentation of informed consent required by HHS and/or FDA regulations must be satisfied before the IRB will approve a research study, unless the IRB waives or alters the requirements as provided in further detail below.

An IRB may require that additional information be given to participants when, in the IRB's judgment, the information would meaningfully add to the protection of participant rights and welfare.

If vulnerable populations are included in the study, additional standards related to informed consent must be applied. See Part 7, Section II of this OM for details.

2) Short Form Consent Process

The IRB may approve a short form written consent document in certain circumstances. Refer to Part 6 of this OM for additional information.

3) Informed Consent Waivers, Alterations, Exceptions, and Substitutions

In some cases, an IRB may approve a consent procedure that does not include, or that alters, some or all of the required elements of informed consent, or may waive the requirement to obtain informed consent. The IRB must document its findings justifying the waiver or alteration of informed consent.

The following standards apply to all federally and non-federally supported human research that is not FDA regulated. Different rules for FDA-regulated studies are found further below.

Note: U-M has not implemented broad consent for storage, maintenance, and secondary research with identifiable private information or identifiable biospecimens per 45 CFR 46.116(d) and therefore regulatory requirements related to the waiver or alteration of broad consent per 45 CFR 46.116(e) are not applicable.

Waiver or Alteration of Informed Consent

1. An IRB may generally waive or alter the requirements for informed consent only if it finds and documents that:

    a. The research involves no more than minimal risk to the participants;
    b. The research could not practicably be carried out without the requested waiver or alteration;
    c. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
    d. The waiver or alteration will not adversely affect the rights and welfare of the participants; and
    e. Whenever appropriate, the participants or legally authorized representatives will be provided with additional pertinent information after participation.

2. Public Demonstration Project: An IRB may waive or alter the requirements for informed consent in research involving public benefit and service programs if the IRB finds and documents that:

    a. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials; and
    b. The project is designed to study, evaluate or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
    c. The project could not practicably be carried out without the waiver or alteration.

3. Screening, Recruiting, and Determining Eligibility: An IRB may approve a research proposal in which a researcher will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective participants without the informed consent of the prospective participant or the participant's legally authorized representative, if either of the following conditions are met:

    a. The researcher will obtain information through oral or written communication with the prospective participant or legally authorized representative, or
    b. The researcher will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Waiver of Requirement for Parental Permission

For research involving children as participants, an IRB may waive the requirement to obtain parental permission if it finds and documents that:

1. The research involves no more than minimal risk to the participants;

2. The waiver or alteration does not adversely affect the rights and welfare of the participants;

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

4. The research cannot practicably be carried out without the waiver or alteration;

5. When appropriate, the participants will be provided with additional pertinent information after participation.

Alternatively, the IRB may waive the requirement to obtain parental permission if it finds and documents that:

1. The research is designated for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants; and

2. An appropriate mechanism for protecting the children who will participate as participants in the research is substituted.

Waiver of Documentation of Informed Consent

The IRB may waive the requirement for documentation of informed consent if it finds and documents any of the following:

1. That the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant (or legally authorized representative) will be asked whether the participant wants documentation linking the subject with the research, and the participant's wishes will govern;

2. The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context; or

3. If the participants or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to participants and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Even if the IRB approves a waiver of documentation of consent, the IRB will review a written description of the information provided to participants and may require the researcher to provide subjects with a written statement regarding the research.

For emergency research, the IRB may approve a waiver of consent consistent with the guidelines found at https://research.medicine.umich.edu/office-research/institutional-review-boards-irbmed/guidance.

4) Studies Subject to FDA Regulations

Waiver or Alteration of Informed Consent

1. Per guidance, the FDA has indicated that an IRB may waive or alter the requirements for informed consent if it finds and documents that:

    a. The clinical investigation involves no more than minimal risk to the participants;
    b. The clinical investigation could not practicably be carried out without the requested waiver or alteration;
    c. The waiver or alteration will not adversely affect the rights and welfare of the participants; and
    d. Whenever appropriate, the participants or legally authorized representatives will be provided with additional pertinent information after participation.

2. Emergency Use of a Test Article Prior to IRB Review and Approval: An IRB may waive or alter the requirements for informed consent in certain emergency situations, if it finds and documents that certain requirements have been met.

    a. When the IRB receives a request to use an investigational agent without informed consent, the IRB will assess whether or not the regulatory criteria set forth in 21 CFR 50.23 apply. See IRBMED guidance: Emergency Use of a Test Article in Life Threatening Situations
    b. Where the IRB is informed after the use of an investigational agent without informed consent, the IRB will assess whether or not regulatory criteria in 21 CFR 50.23 were followed.

See Part 12 of this OM for potential corrective action measures in response to non-compliance.

3. Exception from Informed Consent for Planned Emergency Research: In reviewing a study that requests an "Exception from Informed Consent Requirements for Emergency Research," the IRB will assure that the criteria set forth in 21 CFR 50.24 described are met.

Waiver of Documentation of Informed Consent

The IRB may waive the requirement for documentation of informed consent if it finds and documents the following:

1. That the research presents no more than minimal risk of harm to participants; and

2. That the research involves no procedures for which written consent is normally required outside of the research context.

Even if the IRB approves a waiver of documentation of consent, the IRB will review a written description of the information provided to participants and may require the researcher to provide participants with a written statement regarding the research.

5) Studies Subject to Both HHS and FDA Regulations

The following tables may be referenced when a study is regulated by both FDA and HHS regulations. Tables 3 and 4 compare the types of waivers or exceptions that may be requested by a researcher under one agency's regulations and determine if it can be approved if the other agency also has jurisdiction.

Table 3: Comparison of FDA Criteria to HHS Criteria

HHS OHRP criteria are met	General Waiver or Alteration of Consent 45 CFR 46.116 (f)	Waiver, Alteration, or Substitution of Parental Permission 45 CFR 46.116(f); 45 CFR 46.408(c)	Waiver of documentation of informed consent 45 CFR 46.117 (c)
Applicability if the study is regulated by FDA	Allowed if the following criteria are met: • The clinical investigation involves no more than minimal risk to the subjects; • The clinical investigation could not practicably be carried out without the requested waiver or alteration; • The waiver or alteration will not adversely affect the rights and welfare of the subjects; and • Whenever appropriate, the subjects, or legally authorized representatives will be provided with additional pertinent information after participation. See 2017 FDA Guidance	Waiver, alteration or substitutions are not allowed for the aspects of the project that meets the FDA definition of research.	Allowed if both apply: • Study is minimal risk; and • Involves no procedures for which written consent is normally required outside the research context. 21 CFR 56.109 (c)(1)

Table 4: Comparison of HHS Criteria to FDA Criteria

FDA criteria are met	FDA Emergency Use Exception 21 CFR 50.23 (a)	FDA Emergency Research Exception 21 CFR 50.24	FDA Terrorism/ Public Health Emergency Exception 21 CFR 50.23 (e)	FDA/DOD Presidential Waiver for Military 21 CFR 50.23 (d)
HHS OHRP applicability if the study is supported by federal funding.	Agent can be administered but data collected cannot be used for research.	Allowed if informed consent is obtained after the research is initiated.	Allowed if 46.116(d) applies.	HHS has not provided specific guidance. The IRB should consult with the IO or DIO in the event this waiver is requested.

6) Studies Subject to the Health Insurance Portability and Accountability Act (HIPAA)
Under HIPAA regulations, researchers must obtain written authorization from a research participant for the use, or disclosure of protected health information for the study unless one of the following applies:

a. Waiver or alteration of authorization approved by the IRB;
b. Use of limited data set shared under the terms of a written data use agreement;
c. Research solely on the protected health information of decedents (deceased individuals); or
d. Preparatory to research activities, such as assessing the feasibility of conducting a study.

See additional IRBMED guidance: Use and Disclosure of Protected Health Information

Waiver or Alteration of HIPAA Authorization

The IRB may waive or alter the requirement to obtain written authorization if the IRB finds and documents all of the following:

1. The use or disclosure of protected health information involves no more than minimal risk to the participants' privacy, as demonstrated by:

   a. An adequate plan to protect any identifiers from improper use or disclosure;
   b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research (unless there is a health or research justification for retaining the identifiers or retention is required by law); and

c. Adequate written assurances that the protected health information will not be reused or disclosed except as required by law or for research oversight or for other research approvable under a waiver.

2. The research could not practicably be conducted without the waiver; and

3. The research could not practicably be conducted without access to and use of the protected health information.

f. Data and Safety Monitoring

SOPs must provide that the IRB will ensure, when appropriate, that research plans make adequate provision for monitoring data collected to ensure participant safety and describe how the IRB makes this determination. Additional information on data and safety monitoring plans is available in Part 7 (II) of this OM.

g. Privacy and Confidentiality Protection

"Privacy" refers to the willingness of research participants to allow access to themselves and their information. "Confidentiality" refers to the agreement between the researcher and participants on how the participants' identifiable private information will be managed and used. SOPs must provide that the IRB will ensure that research plans make adequate protections for safeguarding participant privacy and confidentiality. See U-M HRPP Guidance: Privacy and Confidentiality Protections in Human Research for additional information.

h. Vulnerable Subjects

SOPs must describe the different standards that apply to research involving vulnerable populations. These groups include but are not limited to: children, pregnant women, fetuses and neonates, prisoners, individuals who are cognitively impaired or lack decision-making capability, economically or educationally disadvantaged persons, or employees, students or patients of researchers. The IRBs will comply with the standards described in Part 7 (IV) of this OM for review and approval of research involving these populations. These standards limit the categories of research that may be performed and require, as appropriate, additional safeguards to protect participant rights and welfare when they do participate. Additional information is also available in Part 11 of this OM.

i. Test Article Accountability Procedures

SOPs must provide that:

1) The IRB may not approve an application for research involving drugs, biologics or devices unless it determines that the test articles will be used only in approved research protocols, under the direction of approved reseachers, or in emergency circumstances, consistent with FDA requirements and University policies on emergency use;

2) Protocols must describe local drug/biologic or device accountability procedures, if applicable, including procedures required by:
   a. Michigan Medicine Research Pharmacy (formerly Investigational Drug Service (IDS)); and
   b. UMHS Clinical Engineering

3) Investigational drug management and accountability is performed according to Department of Pharmacy Services Policies 400.00-400.10;

4) Investigational device accountability, under most circumstances, is performed by the PI and study teams, who are responsible for documenting the processes for handling and dispensing of investigational devices according to the plan approved by the IRB. Note that investigational devices may need to undergo additional quality control measures to ensure they are safe, and may need to be registered with the University.

j. Resources

SOPs must include provisions requiring IRBs to determine that research studies have the resources necessary to protect participants by evaluating all of the following:

1) There is adequate time for the researchers to conduct and complete the research;

2) There are an adequate number of qualified staff;

3) The facilities where the research will be conducted are adequate;

4) Researchers have access to a population that will allow recruitment of the necessary number of participants; and

5) Medical or psychosocial resources that participants may need as a consequence of the research are available.

For certain categories of research that are not federally supported and not subject to FDA regulations, a researcher or IRB may submit a request to the IO or Designee for an exception to any of the above approval criteria, consistent with the provisions of 45 CFR §46.101(i) except that the IO or Designee assumes the role of the HHS Secretary in considering the request.

7. IRBs Reviewing and Monitoring FDA-Regulated Research

IRBs that review FDA-regulated studies must address additional items in their SOPs (details of which are provided in Part 8 of this OM).

D. IRB Administrative Functions

SOPs must describe key IRB administrative functions and requirements in sufficient detail to inform IRB members and staff, researchers, and other stakeholders of the IRB's rules and expectations. These must include, at a minimum, the elements described below in Subsections 1 to 4. To the extent these elements are addressed through this OM or other institution-wide policy, they need only be referenced in the IRB SOPs.

1. IRB Meetings

SOPs must describe requirements for convened IRB meetings, including the following:

a. A majority of the members of the IRB must be present.

b. At least one non-scientist member must be present in order to meet quorum.

c. At least one unaffiliated member, who represents the general perspective of participants, should be present at the majority of meetings in a given year.

d. In order for the research to be approved, it must receive approval by a majority vote of the quorum (as described above). If, during the course of the meeting, quorum is lost, votes may not be taken until it has been restored.

e. When reviewing research involving prisoners, the prisoner representative is present.

f. When reviewing research that involves participants vulnerable to coercion or undue influence, one or more individuals who are knowledgeable about or experienced working with such participants are present.

g. When convened-board review is not required, the SOPs must include details of any process, such as expedited review procedures (as described above) or subcommittee procedures, which may be used to supplement the IRB's review responsibilities.

h. IRB members may agree, during an appropriately convened meeting, to issue conditional approval for a project only if any requested clarifications or modifications are not relevant to the determinations required by the IRB under the Common Rule or its Subparts (45 CFR 46) or, as applicable, FDA regulations (21 CFR 56). If substantive clarifications or modifications regarding the protocol or informed consent documents are required as a condition of approval, approval must be deferred pending subsequent review of responsive material by the convened IRB.

i. An IRB may establish protocols to convene meetings via video conference, teleconference or similar means. Such protocols must provide a means for all participants to receive the meeting materials prior to the meeting and facilitate active and equal participation in the discussion of all protocols. The protocols must further provide that minutes from meetings convened in this manner will reflect that these two conditions have been met, in addition to other required information.

2. Notification of Decisions

SOPs must describe requirements for how the IRB will notify researchers and the University of its decisions, including the following:

a. An IRB will notify researchers in writing of its decision to approve or disapprove a proposed research activity or of modifications to the proposal that are required to secure IRB approval.

b. If the IRB decides to disapprove a research activity, it must include a statement of the reasons for its decision in its written notification and must give the researcher an opportunity to respond in person or in writing.

c. An IRB will notify the IO or designee and other institutional officials, when appropriate, of its decisions regarding proposed research activities by formal or informal means, such as through access to relevant electronic databases.

SOPs must also describe any process for reviewing and acting on researcher responses to IRB actions.

3. IRB Response to Noncompliance, ORIOs, and Other Required Reporting

SOPs must require prompt reporting of ORIO to the IRBs, HRPP Director, IO, designee, and any other institutional officials, as appropriate, including:

a. Any unanticipated problems involving risks to participants or others;

b. Any serious or continuing noncompliance with federal regulations, institutional policy, or IRB requirements; and

c. Any suspension or termination of IRB approval consistent with the requirements of Part 12 of this OM.

SOPs must describe the procedures that the IRB uses to receive, investigate, and address such reports, including the range of actions the IRB may take in response to such reports, consistent with the requirements of Part 12 of this OM. The process for making additional reports to sponsors and government authorities with jurisdiction outside of the institution is described in Part 12 of this OM.

4. IRB Records and Reports

SOPs must describe how the IRB documents its activities and decisions and maintains records of that documentation, including:

a. Copies of:
- Research proposals reviewed;
- Scientific evaluations, if any, accompanying the proposals;
- Approved sample consent documents;
- Recruitment materials;
- Status reports (Scheduled Continuing Review Applications) submitted by researchers;
- Investigator brochures, if any;
- Data and safety monitoring reports, if any;
- Unanticipated problems involving risks to participants or others; and
- Reports of injuries to participants.

b. Records of continuing review activities, including the rationale for conducting continuing review of research that would not require continuing review as described in 45 CFR 46.109(f)(1);

c. Records of modifications to previously approved research;

d. Statements of significant new findings provided to participants;

e. Documentation of non-compliance;

f. Copies of official correspondence between the IRB and researchers;

g. All previous and current rosters of IRB members;

h. Resumes for all IRB members;

i. The rationale for an expedited reviewer's determination that research appearing on the expedited review list is more than minimal risk and requires convened review;

j. Description of the action taken by the reviewer;

k. Documentation of exemption determinations, including the category by which research was determined to be exempt;

l. Documentation of approvals using the expedited procedure; and

m. Minutes of IRB meetings that document compliance with regulatory, institutional, and other applicable requirements.

SOPs must describe IRB record retention mandates and destruction standards, including the following:

a. IRBs must maintain applicable records for at least three years after the completion of the study;

b. If a protocol is terminated without participant enrollment, IRB records are maintained for at least three years after termination;

c. If an IRB performs functions on behalf of a "covered entity" (such as Michigan Medicine) related to HIPAA and research, those records must be retained for at least seven years, either by the IRB or by the covered entity; and

d. Administrative units responsible for IRB operations may impose longer retention and specific destruction standards.

All IRB records maintained must be maintained securely and made accessible for inspection and copying by authorized representatives of the University, relevant sponsors, and government authorities with jurisdiction (such as OHRP, FDA, and National Institutes of Health (NIH)) at reasonable times and in a reasonable manner.

E. Quality Assurance and Quality Improvement

At least once every five years, in conjunction with the AAHRPP accreditation cycle, the UM Office of Research initiates a comprehensive review of the HRPP OM. IRB SOPs must make provisions for such a review of SOPs on the same cycle or more frequently at the IRB's discretion. Revisions to the SOPs may be made at any time, as required by changes in law, ethical standards, institutional policy, quality assurance activities or other considerations. Substantive revisions require advance approval by the HRPP Director. Additional requirements for quality assurance and quality improvement are described in Part 12 of this OM.

IV.OTHER REVIEW UNIT STANDARD OPERATING POLICIES AND PROCEDURES

Other review units listed in Part 2 of this OM must develop, implement, and enforce their own standard operating procedures relevant to their role in the HRPP.

PART 4: Activities Subject to the HRPP

Describes when a particular activity is subject to the University's HRPP, provides examples of not regulated activities, and outlines the policy on exempt research.

I. DETERMINING WHAT IS AND WHAT IS NOT HUMAN SUBJECTS RESEARCH

Research is defined under the Common Rule as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." (See 45 CFR 46.102(l))
For purposes of human subjects research at the University of Michigan, a "systematic investigation" is an activity conducted in pursuit of answering a specific research question or to permit conclusions to be drawn. The research is described in a formal protocol that sets forth an objective and a set of procedures to reach that objective, and results in the formulation of generalizable knowledge based on conclusions drawn. In turn, "generalizable knowledge" is knowledge based on the findings of a particular research study (or studies) that may be applied more broadly with the expectation of predictable outcomes.

The distinction between research and clinical practice, non-research evaluation, journalism, and other activities involving interactions with living individuals or use of their private information may be vague. The Belmont Report illustrates the difference between research and practice in the clinical realm.

In the clinical realm, the term, "practice" generally refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental, innovative, or novel," in the sense of new, untested, or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. The general rule is that if there is any element of generalizable research in an activity, the activity should undergo review for the protection of human subjects.

A "clinical investigation" under FDA regulations generally refers to any experiment that (See 21 CFR 56.102(c)):

- Involves a test article (defined as a drug, biological product, medical device, human food additive, color additive, electronic product, or any other article subject to regulation under the Food, Drug and Cosmetic Act (FD&C Act) or the Public Health Service Act);
- Involves one or more human subjects; and
- Meets the requirements for prior submission to the FDA or whose results are intended to be submitted to FDA as part of an application for a research or marketing permit.

Section III below describes who has the authority to make a determination about whether or not a particular activity constitutes human subjects research subject to the HRPP, provides illustrations, and describes the process for notifying a researcher of the determination.

II. DETERMINING WHETHER RESEARCH INVOLVES HUMAN SUBJECTS

The fact that an activity is research does not mean that it is "human subjects" research under the Common Rule or a clinical investigation under corresponding FDA regulations.

The Common Rule (45 CFR 46.102(e)) defines a human subject as a living individual about whom an investigator (whether professional or student) conducting research:

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

Refer to 45 CFR 46.102 for the definitions of intervention, interaction, private information, identifiable private information and biospecimens.

FDA regulations (21 CFR 56.102(e)) define a "human subject" as an individual who is or becomes a participant in research, either:

- As a recipient of a test article (drug, biologic, or device); or
- As a control.

A subject may be either a healthy individual or a patient. A human subject also includes individuals on whose specimen a device is used.

Research on specimens derived from living individuals may be considered human subjects research under both the Common Rule and FDA regulations and, therefore, for purposes of the University's HRPP. Guidance on whether or not a project involving human specimens may be considered regulated research is available on the following federal websites:

- Office for Human Research Protections Decision Charts
- NIH Office for Extramural Research Human Subjects Research Homepage
- FDA Guidance Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
- FDA 21 CFR 812.3(p)

Private information must be individually identifiable (ie the identity of the participant is or may readily be ascertained by the researcher or associated with the information being collected) in order for obtaining or using the information to constitute research involving human subjects. The following illustrations may assist researchers in determining whether their activities constitute human subjects research:

- A researcher requests a University department to release individually identifiable private information to the researcher for use in a research project. *Because the information is individually identifiable, the research is considered "human research" and the investigator must obtain IRB (Institutional Review Board) approval or verification of exemption before initiating the protocol.*
- A researcher obtains a completely de-identified dataset from an institution or agency outside of the University. The researcher will not make any attempt to re-identify the information contained in the dataset. *The researcher has not received identifiable private information and, therefore, the project is not subject to University IRB approval or HRPP oversight. However, the originating institution may impose additional requirements.*

Determining when information may be considered "de-identified" can be difficult. Privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) provide the standard for de-identification of protected health information by either:

- The “Safe Harbor” method which requires nineteen identifiers be eliminated from a data set to render it "de-identified"; or
- The “Expert Determination” method which requires a statistician to verify that the recipient of the dataset will not, based on the dataset and any other information to which the recipient may have access, be able to re-identify an individual.

See 45 CFR 164.514(b); OCR Guidance on Methods for De-Identification of PHI; National Association for Public Health Statistics and Information Systems, Release of Individual-Level Vital Statistics Records for Research).

The NIH has developed additional guidance in its grant application instructions to help determine when research involves human subjects.

III. DETERMINING WHETHER THE UNIVERSITY IS RESPONSIBLE FOR IRB OVERSIGHT OF HUMAN SUBJECTS RESEARCH

The U-M is responsible for IRB oversight of human subjects research when its *employees or agents* are engaged in the conduct of human subjects research. An institution is considered to be *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain:

- Data about the subjects of the research, including identifiable biospecimens, through intervention or interaction with them;
- Identifiable private information about the subjects of the research; or
- The informed consent of the human subjects for the research.

An institution's employees or agents are individuals who:

- Act on behalf of the institution;
- Exercise institutional authority or responsibility; or
- Perform institutionally designed activities.

Employees and agents can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

The activities and obligations of U-M employees, students, and agents are considered to be “University responsibilities." However, a faculty member who performs outside activities for unrelated institutions and not as part of his/her U-M appointment is not involved in “University responsibilities” in that context. For example, university responsibilities do not include activities performed by Agency Fund organizations (e.g., Alumni Association, MERIT Network, University Musical Society, William Davidson Institute, and others). Therefore, Agency Fund employee activities, including those performed by university employees leased to the external entity, are not considered University responsibilities. Conversely, a faculty member who provides professional services at an outside institution under a contract between the University and the outside institution, and who is paid for his/her work by the University, is performing “University responsibilities.”

If the institution is the direct recipient of an HHS grant for non-exempt human subjects research, it is also considered to be engaged even where all of the human subjects research activities are carried out by another institution.

See OHRP, Guidance on the Engagement of Institutions in Human Subjects Research, 2008 for additional guidance.

When the University collaborates on a research project involving another institution or an outside individual, the U-M IRB may accept oversight for the project and serve as the IRB-of-Record. In addition, U-M may decide to cede oversight to a commercial IRB or another institution's IRB.

IV.DETERMINING WHEN RESEARCH BEGINS AND ENDS

Research begins when a researcher *first* "obtains data through intervention or interaction," or otherwise obtains "private information," as described above. For example, biomedical research begins when a researcher first collects individually identifiable private information about potential participants, contacts those individuals, or performs eligibility testing solely for research purposes. Because the initial data access and contact constitute research, an IRB must review and approve the proposed data access and communication in advance.

Research is considered to continue and IRB approval must remain active through data collection, while personally-identifiable data are being analyzed, or as long as there is intent to conduct long-term follow-up on participants of the currently approved research. When IRB approval lapses, expires, or is terminated, no interventions or interactions may occur and no identifiable data may be collected or analyzed, until the project is re-approved by the IRB. See Part 3 of this OM regarding lapse in IRB approval.

Once all personal identifiers and links to identifiers are destroyed, the research is no longer regulated under federal regulations or the University's HRPP.

Secondary analysis of data collected as part of a previous study that retains identifiers must be submitted to the IRB for approval or exemption. The language of the original consent is a factor in the IRB's determination of whether secondary data analysis may be conducted.

V. AUTHORITY TO MAKE REGULATED/NOT REGULATED DETERMINATIONS (PER THE COMMON RULE AND FDA) AND NOTIFICATION OF DECISIONS

A. Authority to Make Regulated/Not Regulated Determinations

The IO has delegated to the IRBs and their staff the authority to make regulated/not-regulated determinations in a manner consistent with their approved standard operating procedures. The IO also has the authority to make a regulated/not-regulated determination for any specific project or category of projects.

The University does not require researchers to seek a formal "Not Regulated" determination from the IRB when the activity falls outside of the Common Rule and FDA definitions of human subjects research or where the University is not engaged in the research. Some types of projects that are not regulated under the Common Rule may require review only for the purpose of assessing compliance with HIPAA or other regulations or institutional policies. Researchers may consult informally with IRB staff or members to facilitate a self-determination. To obtain formal documentation of a "Not Regulated" determination, an "Activities not regulated as human subjects research" IRB application must be submitted in eResearch regulatory management. This application type allows the PI to self-generate a "Not Regulated" determination letter that may be used for funding or publication purposes or to request an IRB review to confirm the status of the project.

B. Illustrations

The HRPP Leadership has developed the following list of common activities for which categorical regulated/not-regulated determinations have been made; some of these categories are "deemed not to be research" under Federal Common Rule 45 CFR 46.102(l). See also Part 5 of this OM for additional examples of research-related activities

considered to constitute “engagement” or “non-engagement” in research. Selected activities that often are particularly difficult to categorize are discussed in further detail below.

Table 5: Regulated vs. Not Regulated Human subjects research. Activities Requiring or Not Requiring IRB Review and Approval Prior to Initiation

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
Clinical Investigations	Experiments using a test article (eg investigational drug, device, or biological) on one or more human subjects, or on the specimen of a human subject, that are regulated by the FDA or support applications for research or marketing permits for products regulated by the FDA. Products regulated include foods, including dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products that aid in diagnosis or treatment of injury or illness.	YES
Medical Practice	Standard practice, innovative care, or off-label use of FDA-approved drugs, biologics, devices and other articles or substances that are used in the normal course of medical practice, provided the activity does not involve systematic collection of safety or efficacy data, and is limited to prevention, diagnosis, mitigation, treatment, or cure of disease in affected individuals.	NO
Standard Diagnostic or Therapeutic Procedures	The collection of data about a series of established and accepted diagnostic or therapeutic procedures, or instructional methods for dissemination or contribution to generalizable knowledge.	YES
	An alteration in patient care or assignment for research purposes.	YES
	A diagnostic procedure added to a standard treatment for the purpose of research.	YES

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
	An established and accepted diagnostic, therapeutic procedure or instructional method, performed only for the benefit of a patient or student but not for the purposes of research. (See Case Studies)	NO
Public Health Surveillance Activities	Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in disease, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). See 45 CFR46.102(l)(2) .	NO
Case Studies - Clinical	Report about one or two clinical experiences or observations identified in the course of clinical care, provided that FDA regulations requiring IRB approval do not apply, such as use of: ● articles (eg drugs, devices, biologics) that have not been approved for use in humans; ● articles requiring exemption from FDA oversight; or ● articles under an Investigational New Drug Application (IND)/Investigational Device Exemption (IDE).	NO
Case Studies - Other	Report about experiences or observations associated with one or two individuals.	NO
Innovative Procedures,	Systematic investigation of innovations in diagnostic, therapeutic procedure or instructional method in multiple	YES

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
Treatment, or Instructional Methods	participants in order to compare to standard procedure. The investigation is designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge.	
	The use of innovative interventions that are designed solely to enhance the well-being of an individual patient or client and have a reasonable expectation of success. The intent of the intervention is to provide diagnosis, preventive treatment, or therapy to the particular individual. (See Case Studies)	NO
Pilot Testing	Preliminary activities typically designed to help the researcher refine data collection procedures. Pilot testing is considered to be a research activity as defined in 45 CFR 46.102(l); "research means a systematic investigation, including research development, testing, and evaluation."	YES
Repositories (e.g., data, specimens, etc.)	A storage site or mechanism by which identifiable human tissue, blood, genetic material or data are stored or archived for research by multiple researchers or multiple research projects.	YES
Pre-Review of Clinical Data Sets	Activities (eg review of medical data, queries, etc.) intended only to assess the feasibility of future research. Note that Michigan Medicine or other "covered entity" might need to obtain researcher representations for a review preparatory to research for HIPAA compliance purposes.	YES *(required by HIPAA regulations)*
Research involving Coded Biological Specimens/Coded Private Information	Analysis of coded human specimens or coded private human data where: • The specimens/data were not collected specifically for the proposed study through an interaction or intervention with living individuals; • The researchers cannot readily ascertain the identities of the individuals from whom the	YES *(required by HIPAA regulations)*

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
	specimens/data were obtained either directly or indirectly through the coding system because, for example: ○ The researchers and the holder of the key enter into an agreement prohibiting the release of the key to the researchers under any circumstances, until the individuals are deceased (HHS regulations do not require IRB review and approval for this agreement); ○ There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the researchers under any circumstances, until the individuals are deceased; or, ○ There are other legal requirements prohibiting the release of the key to the researchers, until the individuals are deceased; and • The investigator is not a researcher or collaborator on the specimen or data provider's research. For use of specimens, the research must not be testing a drug or biologic in support of an IND application. Use of specimens or data may require HIPAA compliance review.	
U-M functioning as the Coordinating Center for a Multi-Center Research Project	U-M *is not* an enrolling site and the U-M PI has agreed to serve as the coordinating center for a multi-center project, which may include activities such as data collection, data analysis, reporting of adverse events to regulatory authorities, and/or oversight of the research at participating sites.	YES
	U-M *is* an enrolling site and the U-M PI has agreed to serve as the coordinating center for the multi-center project, which may include activities such as data collection, data analysis, reporting of adverse events to regulatory	YES

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
	authorities, and/or oversight of the research at participating sites.	
Emergency Use of an Investigational Drug or Device	Institutional policies do not permit research activities to be started, even in an emergency, without prior IRB acknowledgement. 1. This does not limit the physician's ability to deliver emergency care. The physician may deliver such care, but the data derived from such care may not be used in any prospectively conceived research. 2. Emergency care involving investigational drugs, devices or biologics must meet the FDA requirements and data from such use may not be used in any manner of research.	IRB NOTIFICATION
Classroom Assignments/Research Methods Classes	Activities designed for educational purposes that teach research methods or demonstrate course concepts. The activities are not intended to create new knowledge.	NO
Research Using Publicly Available Data Sets	Use of publicly available data sets that do not include information that can be used to identify individuals. "Publicly available" is defined as information shared without conditions on use. This may include data sets that require payment of a fee to gain access to the data.	NO
Research on Organizations	Information gathering about organizations, including information about operations, budgets, etc. from organizational spokespersons or data sources. Does not include identifiable private information about individual members, employees, or staff of the organization.	NO
Scholarly and Journalistic Activities	Activities (eg oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom their information is collected. (See 45 CFR 46.102(l)(1))	NO *(but exercise of professional ethics is expected)*

ACTIVITIES	DESCRIPTION	SUBMISSION REQUIRED TO IRB
Quality Assurance and Quality Improvement Activities - Clinical or Procedures	Systematic, data-guided activities designed to implement promising ways to improve clinical care, patient safety and health care operations. The activity is designed to bring about immediate positive changes in the delivery of healthcare, programs, or business practices in the local setting.	NO
Quality Assurance and Quality Improvement Activities - Non-Clinical	Data collected with the limited intent of evaluating and improving existing services and programs or for developing new services or programs. Examples include teaching evaluations or customer service surveys.	NO
Research Involving Only Decedents	Research involving only data or tissue obtained from individuals who are deceased prior to the conduct of the research. There must not be any interaction or intervention with living individuals, or collection of private data or specimens associated with living individuals. Note that Michigan Medicine or other "covered entity" might need to obtain researcher representations for research involving decedents' data for HIPAA compliance purposes.	YES *(required by HIPAA regulations)*
Research Involving De-identified Biological Specimens or Information	Research involving a de-identified set (data/biospecimens) which cannot be "re-identified" by any known entity.	NO

Federal regulations also consider certain activities for criminal justice or criminal investigative purposes and agency operational activities to not be research. See 45 CFR 46.102(l) for additional information.

C. Student Practicums and Internships

Many of the professional schools within the University actively seek opportunities for their students to become involved in “real world” activities or work assignments that will introduce them to and, in some cases, provide practical experiences in their chosen profession. This involvement may take the form of an internship requirement. In other situations, the opportunities may come in the form of a “practicum” in which students are assigned to work “in the field” (eg, in a government agency or in industry) to see firsthand how problems are addressed by professionals in their chosen field. The student intern is under the day-to-day direction of the sponsoring organization, may be given specific work assignments, and may work side-by-side with regular employees of the organization. A faculty member,

in turn, provides the "bridge" between the work experience and the learning experience – giving guidance to the student and striving to place the fieldwork into the broader context of the student's educational program.

In general, the development and acceptance of formal University agreements for student practicums or internships are acceptable when, in the opinion of the head of the department in which the practicum would be conducted, the activity may be of educational value or lead to an extension of knowledge, or increase effectiveness in teaching, or increase effectiveness in research. Some student practicums/internships include research activities that are designed to contribute to generalizable knowledge and, thus, are research and reviewable by the IRB. Some are not. The following table illustrates the distinctions between activities that do and do not require IRB review.

Table 6: When is U-M IRB approval required for student practicums or internships?

CIRCUMSTANCE		U-M IRB REVIEW REQUIRED?
A practicum/internship that falls within the work scope of a local, state, or federal agency (eg Public Health Agency) or employment by private industry involving data collection for non-research purposes. No *a priori* research design or intent.		NO
Use of or access to human subjects data previously collected for non-research purposes (perhaps through a circumstance like the one above) in a systematic investigation designed to contribute to generalizable knowledge, one indicator of which is publication.		YES
Participation with or providing services to a U-M PI conducting IRB-approved research. No work outside the scope of the IRB approval.	Student is providing research assistance at the level not normally requiring an IRB project amendment. For example, providing administrative support for manuscript preparation or working with a fully de-identified data set.	NO
	Student is providing research assistance at the level of key personnel. For example, accessing identifiable data/biospecimens or interacting with participants for the purposes of the research.	YES *(Amendment required.)*
U-M Student is participating with or providing services to a non-UM research project. Research is approved by a non-UM IRB.	Requires a confirmation letter from the non-UM PI if the student is **not engaged** in the conduct of human subjects research. The letter should be maintained in the student file by the student's U-M faculty mentor.	NO

CIRCUMSTANCE		U-M IRB REVIEW REQUIRED?
	U-M IRB Authorization Agreement ceding oversight to non-UM IRB or IRB review at U-M is necessary if the student is **engaged** in the conduct of human subjects research.	YES
Independent research project not falling within the scope of a previously approved project.		YES *(Faculty member assigned as faculty advisor is ultimately responsible.)*

If a student or faculty member is unsure whether a particular activity requires U-M IRB approval, they should contact the U-M IRB that traditionally monitors research conducted within their academic unit. See Part 5 of this OM to determine the correct IRB.

D. Notification of Decisions

When a human subjects research/not human subjects research determination is made the person requesting the determination is informed by electronic confirmation.

VI. POLICY ON EXEMPT RESEARCH

A. Introduction

Under certain circumstances, human subjects research activities subject to the HRPP may be granted exempt status (45 CFR 46.104). This means a study is considered to be research with human subjects, but if it meets the criteria for one or more of the exemption categories, the research is not subject to *all* of the regulatory requirements of 45 CFR 46. For some exemption categories, the regulations require a "limited IRB review" and/or Privacy Board review of the initial application as part of the exemption determination. Researchers are not required to return to the IRB for approval of amendments to exempt studies, except where changes to the study take the project outside the scope of the original exemption. *Exempt status does not, however, lessen the ethical obligations to subjects as articulated in the Belmont Report and in disciplinary codes of professional conduct.*

IRB SOPs require an IRB application be submitted for exempt projects. The application includes specific questions to evaluate the protection of human subjects and to determine eligibility under each exemption category listed in section B. The IRB application is configured to permit researchers to self- generate an exempt determination letter for certain exemption categories based upon responses to qualifying questions. Researchers may also choose to submit these applications to the IRB for review. All other applications for exemption are reviewed and determinations issued by the IRB or IRB staff. Exemption applications requiring limited IRB review are evaluated via the expedited review process for assessment of provisions for subject privacy and confidentiality of data found at 45 CFR46.111 (a)(7) before an exemption determination is made.

The applicable exemption category or categories are recorded in the eRRM system and included in the determination letter issued to the researcher. The application and determination letter remind researchers of the ethical obligation to ensure that participants are fully informed about the nature of a research project so that they can make an informed decision to participate.

B. Categories of Eligibility for Exempt Determination

It is the policy of the University that to be determined to be exempt, research must pose **no more than minimal risk** and the IRB does not determine that continuing review would enhance protection of research participants.

1. Federal Exemption Categories

For a list and detailed requirements of the federal exemption categories see 45 CFR 46.104.

Each of the federal exemption categories may be applied to research subject to 45 CFR 46, Subpart B (*Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research*) if the conditions of the exemption are met. (45 CFR 46.104(b)(1))

Exempt status is not granted for research subject to 45 CFR 46, Subpart C (*Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*), except where the research is intended for a broader subject population and only incidentally involves prisoners. (45 CFR 46.104(b)(2))

Exemptions 1, 4, 5, 6, 7, and 8 may be applied to research subject to 45 CFR 46, Subpart D (*Additional Protections for Children Involved in Research*). 45 CFR 46.104(b)(3) indicates special limitations in the application of exempt status to research with children for exemption 2(i) and 2(ii). Exemptions 2(iii) and 3 cannot be applied to research with children. Those exemption categories with limitations for research involving children are also noted below.

FDA-regulated research may not be granted exempt status, except for Exemption 6 listed below. Subject to the exceptions above, and consistent with IRB-specific SOPs, research may be granted exempt status if all proposed research activities involve procedures listed in one or more of the specific categories below. (See 45 CFR 46.104.)

For Exemptions 2, 3, 7, and 8, in order for the IRB to conduct limited review, the researcher is required to submit information as part of the eResearch application, including:

- A protocol document or a protocol summary that describes the participant population, study procedures, and research locations;
- Documents relevant to the research (e.g. recruitment materials, a proposed consent document, survey instruments); and
- Information regarding the sensitivity of data to be collected.

Note: U-M has not implemented Broad Consent and therefore exemption categories 7 and 8 are not applicable to U-M research.

2. U-M Exemption Categories

The following exemption is defined by U-M policy (see HRPP Flexibility Initiatives):

- U-M Exemption 5: Research and demonstration projects sponsored by the State of Michigan 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 under those programs.

C. Authority to Grant Exempt Status

The IO has granted to the University IRBs the authority to invoke federal exemptions 1-4 and 6-8 listed at 45 CFR 46.104. How and to whom the IRBs in turn distribute the authority to issue exemptions is described in their SOPs. IRB SOPs will ensure that individuals issuing exemptions receive initial and continuing training in the details of the exemption process.

The IO allows the IRBs, consistent with their SOPs, to permit researchers to self-generate an exemption determination letter based upon responses to qualifying questions. System-generated exemption determinations may be subject to audit the by IRBs or the HRPP to validate the outcome. Research eligible for system-generated exemption determination must meet the criteria for exemption categories 1-3 and is subject to the following limitations:

- The research does not involve any data subject to HIPAA or FERPA regulations;
- For Exemption 3, the research cannot involve deception or concealment;
- The research does not require "limited IRB review" under 45 CFR 46.104.

The IRB does not grant Exemption 5. The IO has delegated the authority to grant Exemption 5 (Federal and U-M Exemption 5) to the HRPP Director. Any project that may be eligible for Exemption 5 will be forwarded to the HRPP Director for review.

D. Notification and Documentation of Exempt Status

The person requesting the exempt determination is informed by electronic confirmation. The notice of exempt determination includes the exemption category assigned to the project and a statement that an amendment must be submitted to the IRB for any change in the research that **might affect exempt status**. The amendment must be submitted before the change is initiated.

Part 5: IRB Jurisdiction, Cooperative Research, and Reliance Agreements

Describes the scope of jurisdiction of the various University IRBs and policies on cooperative research and IRB reliance agreements.

I. INTRODUCTION

The U-M has registered eight IRBs under its Federalwide Assurance with the U.S. Department of HHS. Two IRBs (collectively referred to as IRB-Health Sciences and Behavioral Sciences, or IRB-HSBS), are operated by UMOR and review health, behavioral, educational, and social science research outside of Michigan Medicine (formerly known as the University of Michigan Health System, or UMHS), including research from the U-M Dearborn and Flint campuses. Six IRBs (collectively referred to as IRBMED) review Michigan Medicine (including U-M Medical School) research, U.S. FDA regulated research, and research using Michigan Medicine protected health information. This section of the OM describes the scope of jurisdiction of these various University IRBs and outlines University policies on cooperative research and reliance agreements when sharing oversight of research with another institution.

II. WHICH UNIVERSITY OF MICHIGAN IRB

The guidance below describes in more detail default IRB jurisdiction, common exceptions, and the procedures to follow in determining jurisdiction in unusual cases. For any transfer, the receiving IRB will be provided with all information associated with the review by the original IRB via eResearch.

A. IRBMED

1. Primary Jurisdiction

- All research proposed by faculty, staff, students or trainees affiliated with Michigan Medicine, including the Medical School
- All research using the patients, medical records, or facilities of the University of Michigan Health System
- All FDA regulated research
- All clinical investigations conducted by School of Dentistry
- Research using the Functional MRI (fMRI) Laboratory, except for researchers under IRB-HSBS jurisdiction that conduct social/behavioral projects using the IRBMED-approved fMRI Master Protocol

2. Exceptions

By agreement of the IRBs, IRB-HSBS may review some categories of exempt research submitted by Medical School researchers, and recruitment activities involving Michigan Medicine patients but do not involve the conduct of the research within a Michigan Health System facility or access to medical records.

B. IRB-Health Sciences and Behavioral Sciences

1. Primary Jurisdiction

All research conducted by the faculty, staff, students or other trainees with a primary appointment in U-M Ann Arbor schools, colleges, units or programs, or with U-M Dearborn or Flint and not subject to IRBMED jurisdiction. These include but are not limited to:

- U-M Institutional Research
- U-M Ann Arbor campus units:
  - College of Architecture and Urban Planning
  - College of Engineering
  - College of Literature, Science, and the Arts
  - College of Pharmacy
  - Institute for Social Research (ISR)
  - Ford School of Public Policy
  - Law School
  - Mary A. Rackham Institute
  - Rackham Graduate School
  - Ross School of Business
  - School of Dentistry
  - School of Education
  - School of Environment and Sustainability
  - School of Information
  - School of Music, Theatre, and Dance
  - School of Kinesiology
  - School of Nursing
  - School of Public Health
  - School of Social Work
  - Stamps School of Art and Design
  - University Health Services
- U-M Dearborn campus units:
  - College of Arts, Sciences, & Letters
  - College of Business
  - College of Education, Health, & Human Services
  - College of Engineering & Computer Science
- U-M Flint campus units:
  - College of Arts and Sciences
  - College of Health Sciences
  - School of Education and Human Services
  - School of Management
  - School of Nursing

C. General Exceptions

1. In any case where the IRB with primary jurisdiction determines that it does not have the appropriate expertise or is not appropriately constituted to review a research proposal, the project may be transferred to the IRB with appropriate expertise for review and approval.

2. In those instances, in which COIs preclude a quorum for review, the project may be transferred to an alternate IRB with appropriate expertise for review and approval. The selection of an alternative IRB will be made by the chair of the referring IRB in consultation with the receiving IRB, if the chair does not have a disqualifying conflict. If the chair has a disqualifying conflict of interest, the IO or designee will make the selection.

3. In those instances, in which another IRB or a faculty member, staff member, student, or other trainee requests review by an alternate U-M IRB, the IRB Directors or Assistant Directors will review the reasons

for such a request; and decide which IRB shall conduct the review. The IO may overrule a Director's refusal to refer an application to another U-M IRB.

4. In rare instances, in which the rules outlined in this section do not clearly define which IRB to use and the IRB Directors cannot agree on jurisdiction, the matter may be referred to the IO for a recommendation.

The IRB is also authorized, at its discretion, to invite individuals with special expertise to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals will disclose any conflicts of interest to the IRB and they may not vote with the IRB.

III.COOPERATIVE RESEARCH

Researchers at the U-M frequently interact with entities or individuals outside the University. The types of relationships are too numerous to list, but they may include

- Establishing research collaborations by subcontract from or to the University;
- Serving as the coordinating site for a multi-center clinical trial being conducted elsewhere or serving as a performance site in a multi-center clinical trial;
- Conducting research at clinics, schools, etc., where the outside site provides only access or where the outside site has or will have identified data;
- Conducting research in another country, but not in partnership with an established entity in that country, and establishing relationships with individuals, such as volunteer research assistants, who will provide services.

The University's (and its researchers') regulatory obligations and alternatives for addressing cooperative research situations differ depending on the relationship with the entity or individual outside the University in the context of the research project. In analyzing the many types of relationships that exist between the University and its researchers, on one hand, and outside entities or individuals, on the other, a primary distinction can be made between those that are "engaged" in human research versus those that are not engaged. This distinction is important because each engaged institution is responsible for safeguarding the rights and welfare of research participants and for complying with applicable laws and regulations (including the Common Rule, as appropriate) and with its own HRPP policies and procedures.

The HRPP has implemented the policies described below and in Part 3 of this OM to ensure that the University can fulfill its affirmative obligation to assure appropriate oversight of research in which the University is "engaged" and also, under certain circumstances, of other "engaged" entities associated with University research.

A. Engagement in Human Research

The circumstances under which an institution is considered engaged in research are described in Part 4 of this OM and the OHRP guidance on engagement of institutions.

B. Researcher and IRB Responsibilities with Regard to Engaged Performance Sites

When multiple sites are engaged in non-exempt research, the U-M IRB must approve the arrangements for review. The process for determining the appropriate review arrangements including the use of a single IRB (sIRB) and the circumstances under which the University will agree to serve as IRB-of-Record for other engaged sites or to cede review of University research to other IRBs are described below in section IV and on the IRB websites. When the overall PI of research conducted at multiple locations is affiliated with the University, or the University is otherwise involved as the primary or coordinating center, the PI must assure the University IRB that each performance location involved in the research has requested a Reliance Agreement or that the research has been properly approved at that

location before the research is initiated there and must notify the University IRB if any lapse or other change in approval status occurs. The IRB may take any steps it deems appropriate to verify the information provided by the PI.

C. Researcher and IRB Responsibilities with Regard to Performance Sites not Engaged in Research

When a performance site is not engaged in research, it is the responsibility of the PI to assure that the site's facilities and resources are appropriate for the nature of the activities that will be conducted there. It is also the responsibility of the PI to notify the IRB promptly if a change in research activities changes the performance site's engagement in research.
IRBs may ask researchers to submit statements from entities providing research services or site access but not "engaged" in research to provide evidence of permission by those entities for their involvement. The researcher may begin research activities at each site as it is approved by the IRB. Sites may be added to a research study with the submission of an amendment and the appropriate documents to the IRB for review and approval prior to beginning research activities at the new performance sites.

D. Special University IRB Responsibilities for Multi-Site Research in Which the University is Involved

1. Generally

IRBs whose jurisdiction typically extends to research in which the University is one of multiple engaged sites must have a method to:

- Determine when other IRBs are involved and if sIRB is required;
- Define their respective responsibilities in connection with the research;
- Communicate as appropriate with the other involved IRBs; and
- Notify researchers of any special expectations with regard to the conduct of multi-site research.

This may be accomplished through any combination of SOPs, application forms, formal and informal guidance, inter-institutional agreements, and other communications. For example, the University IRB should determine prior to the initiation of research how it will solicit and review reports of unanticipated problems involving risks to research participants or others, regardless of location, when those risks may have an impact on any matter within that IRB's jurisdiction.

2. University of Michigan as a Lead or Operations Coordinating Center

In general, the Lead Site (also referred to as the Lead Coordinating Center (LCC) or Clinical Coordinating Center (CCC)) has the responsibility for providing administrative oversight, management of data, and the provision of organizational support in the conduct of a multi-site research project. If a U-M faculty is designated as the Lead Site PI for the conduct of a multi-site research project, the IRB will require additional information to ensure there is appropriate regulatory oversight and management, and may suggest the submission of a separate multi-site application in eResearch. Information reviewed by the IRB will include, but is not limited to, the following:

a. Regulatory Documentation

The Lead Site PI should submit a plan to the IRB for managing the regulatory documentation (eg informed consent, protocol amendments, site IRB approvals, etc.) from each of the participating sites. The Lead Site PI must also require each participating site to maintain and manage its own regulatory documentation according to their institutional policies and procedures. The Lead Site PI is also responsible for creating a manual or other relevant documentation (eg a Manual of Operations binder) which contains all the information required by each individual site to complete the study. This manual will be shared with each site.

b. Participating Site Communication Plan
The Lead Site PI should describe the plan for documented communications between the participating sites and the LCC/CCC. Communications may include information on changes to the regulatory documentation (research protocol, informed consent, etc.), interim analysis on the progress of the research project, or safety reporting.

c. Reporting of Serious Adverse Events and Unanticipated Problems
The Lead Site PI is responsible for the development, collection, and maintenance of a plan to review, in a timely fashion, all serious adverse events (SAEs) and unanticipated problems. The Lead Site is responsible for meeting the reporting timelines to the IRB as described in the research protocol, as well as, monitoring the participating sites reporting obligations to their own IRB and the U-M Lead Site.

d. Data Collection and Analysis (Data Coordinating Center (DCC))
The Lead Site PI is responsible for either the development of case report forms (CRFs), or other data collection instruments, or delegating the task to another site (eg DCC). The Lead Site PI is also responsible for managing retention of documents according to institutional or sponsor policies and procedures. If the Lead Site PI also has the responsibility of data coordination, then he/she should submit a separate application in eResearch for the functionality of the DCC and provide the IRB with a plan for the review of the study data and the submission of any required interim analysis results sent to participating sites.

e. Participating Site Training
The Lead Site PI should confirm that all participating sites have received appropriate human subjects research training for the conduct of the project and understand the regulatory reporting requirements. In general, the Lead Site PI should ensure that the participating sites are familiar with the research project design and procedures, reporting of SAEs and unanticipated problem(s), administration and documentation of study drug or device dispensation, compliance monitoring, and record retention.

f. Additional Responsibilities
The Lead Site PI should also determine the plan for delegation of authority within the study team and the participating site(s), for ongoing project management as necessary. The Lead Site PI is responsible for ensuring appropriate IRB approval is obtained by sites prior to initiation of the project at that site.

IV.IRB RELIANCE AGREEMENTS

NIH policy, the Common Rule, and certain sponsors require that multi-site and collaborative research use a sIRB model. When one IRB acts as the Reviewing IRB on behalf of other institutions, referred to as Relying IRBs, a written reliance agreement (also called an IRB Authorization Agreement) among the involved institutions is required. Whether using a single IRB or conducting duplicate review when appropriate, the U-M IRB must approve the arrangement either for individual studies or categorically (eg Master Agreements with commercial IRBs). The University does not enter into Reliance Agreements with external entities for projects that have been determined to be exempt.

Note: See FDA Policy on "Non-Local IRB Review" for additional guidance on cooperative research and reliance on non-local IRBs for approval of FDA-regulated research.

A. IRB-of-Record

An IRB is considered the IRB-of-Record when it assumes IRB responsibilities for another institution. In appropriate circumstances, described on the IRB website, the University will consider becoming the IRB-of-Record for the engagement in research by an outside entity or ceding authority for review and oversight of University research, in whole or in part, to an outside IRB. Federally-funded studies require a formal agreement between the institutions

approved by the IOs or their designee(s). The agreement will include the applicable responsibilities listed below and any applicable requirements set forth by accreditation standards.
The IO has delegated authority for approving IRB reliance agreements to the HRPP Director.
IRBs have a central role in determining whether proposed arrangements preserve and promote protections for human participants in research for which they have responsibility, and, thus, are acceptable.

1. Statement of Principles

Under certain circumstances the University will agree to become the IRB-of-Record for research conducted at another entity or allow another institution's IRB to serve as IRB-of-Record for University research. The University will not normally provide IRB-of-Record services for research in which the University is not engaged or in which its researchers are not otherwise involved. Nor will the University provide IRB-of-Record services for research over which the University does not feel it can appropriately address the local context or otherwise exercise adequate oversight. Researchers must obtain approval prior to seeking review by another IRB. When possible, the University prefers to cede oversight to an accredited IRB.

Additional information is provided on the HRPP website.

2. Responsibilities of the Reviewing IRB

- Review of initial submission, continuing review and review of amendments and reportable events for all sites;
- Ensure that local context information provided by relying sites (such as state or local laws, conflict of interest determinations, and site-specific information requested for certain sections of the informed consent) satisfies IRB approval criteria;
- Make Privacy Board determinations per HIPAA, when applicable;
- Review COI management plans provided by the relying institution and, if needed, require modifications;
- Communicate all IRB findings and determinations in writing to researchers, institutions, sponsors, and federal agencies, as appropriate. This includes: decisions on protocols, changes, suspensions, terminations or research participant continuation during lapses in approval, unanticipated problems involving risks to research participants or others, noncompliance, audits, or complaints; and
- Make its policies and procedures available to relying institutions, when applicable and upon request.

3. Procedures for a University IRB to Become IRB-of-Record for Another Institution

Upon receiving a request for IRB-of-Record services, the IRB reviewing the request must decide whether it wishes to accept the obligation. In such a review the IRB should consider any relevant information including, for example:

- The time and resources required to accept the review, given other demands;
- The expertise required for initial and continuing review;
- The ability to comply with requirements for "local" knowledge of the research context at the outside organization and any research sites;
- The resources, ability, and willingness of the outside organization, the PI, and the research sites to handle complaints, review adverse events, and to monitor compliance with applicable laws and regulations and IRB requirements; and
- The ability and willingness to comply with any additional requirements the outside organization may impose on the U-M review.

If the U-M IRB agrees to accept the responsibility, the HRPP Director will prepare a recommendation based on the IRB's willingness to provide services and any other relevant institutional-level factors, including the ability to manage any potential conflict of interest. An arrangement to accept responsibility as the IRB-of-Record must

be documented in a written agreement under which the respective responsibilities of the two organizations will be described. An inventory of such agreements is maintained by the HRPP.

4. Responsibilities of the Relying IRB

- Identify and provide local considerations to the reviewing IRB, related to state or local laws, and institutional policies and/or standards;
- Identify and analyze COIs, and propose management plans, if needed;
- Provide local ancillary and institutional approvals to the reviewing IRB;
- Ensure research personnel are appropriately trained to conduct human research;
- Ensure research personnel are notified of their responsibilities when conducting research pursuant to a reliance agreement;
- Comply with the determinations and requirements of the reviewing IRB;
- Have access to a Quality Assurance and Quality Improvement (QA/QI) program to ensure proper monitoring of research and perform audits upon request from the reviewing IRB-;
- Have a mechanism by which complaints about the research can be made by local research participants and others; and
- Ensure study team notifies the reviewing IRB of:
  - Unanticipated problems;
  - Serious and/or continuing noncompliance;
  - Restriction/suspension of study team activities;
  - PI and personnel changes;
  - Changes that require informed consent or HIPAA revisions;
  - Audits and inspections, including findings and corrective actions;
  - Communication with regulatory agencies;
  - Institutional legal requests and claims; and
  - Research misconduct.

5. Procedures for Ceding Authority to Another IRB

Requests to cede U-M IRB authority to the IRB associated with another entity, to a commercial IRB, or to a central IRB generally arise in U-M IRB offices in the context of IRB review of projects under their jurisdictions. Requests typically involve oversight of a single project.

First review of a request to cede authority resides with the U-M IRB with jurisdiction. Among the considerations involved in review of a request to cede authority are the following:

- The requirement to cede to an external IRB that is designated as the single IRB-of-Record for a federally-sponsored research project;
- The reduction of regulatory and administrative burden by ceding review to an external IRB;
- The appropriateness of the external IRB to review local context; qualifications of the IRB to which the review will be ceded (with due consideration given to such objective factors as accreditation status); and level of confidence in its review and determinations; and
- The proposed arrangements for monitoring the outside review and oversight.

When reliance on a non-accredited IRB is proposed, the evaluation may involve additional considerations, based on the risks of research, the research activities that the University will be involved in, and the assessed experience and regulatory knowledge of the external IRB. Such considerations include, but are not limited to, review of IRB rosters for identification of areas of expertise, and the University's prior experience with the external IRB.

Final approval of ceding requests is the responsibility of the HRPP Director who will authorize the IRB to establish a formal agreement between the University and the entity in which the external IRB resides (if one

does not already exist), under which the respective responsibilities of the two organizations will be described. The IRB may follow procedures according to established master agreements or prior agreement with the U-M IRB for specified project types or study networks.

6. SMART IRB

U-M is a signatory to the SMART IRB Master Reliance Agreement. The agreement is designed to streamline and harmonize the IRB review process for multi-site studies and eliminate the time and effort of negotiating IRB reliance agreements for each new study. When possible, U-M will use the SMART IRB agreement as the basis for reliance when serving as the sIRB or being a relying IRB of a SMART IRB study.

B. Responsibilities of the HRPP and Local IRB in Multi-Site Research

Even when the University or another institution serves as IRB-of-Record for multi-site research, each organization remains responsible for maintaining a system to protect research participants. The ceding institution retains responsibility for the compliant conduct of research occurring at its site, including safeguarding the rights and welfare of research participants and for educating members of its research community to establish and maintain a culture of compliance with applicable laws and regulations and with institutional policies relevant to the protection of research participants. The ceding institution also remains responsible for implementing appropriate oversight mechanisms to ensure compliance with the determinations of the reviewing IRB. Thus, for example, a U-M performance site may be subject to not-for-cause compliance reviews and for-cause inspections through the University's HRPP even if oversight of the project has been ceded to an outside IRB.

V. UNAFFILIATED INVESTIGATORS

Researchers engaged in federally-funded research conducted by or at U-M who are not who are not employees of the University and not agents of an outside entity that can provide IRB review must sign an "Individual Investigator Agreement" to assure that they understand their obligations as researchers (the IRB may grant an exception in cases involving literacy or technology constraints.) See Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction of the Individual Investigator Agreement.

For non-federally-funded research, unaffiliated researchers generally are required to sign an "Individual Investigator Agreement" but may be granted an exception by the IRB in limited cases. See the flow diagrams for IRB authorization agreements and individual investigator agreements.

VI.COMMUNITY BASED PARTICIPATORY RESEARCH

In certain studies, local community members may be involved in the conduct of U-M human subjects research, such as assisting in the development of the research protocol and study materials, implementation of the research, and dissemination of the research results. Community members engaged in the research and participating on a U-M study team sign an agreement that outlines their roles and responsibilities, identifies training and reporting requirements, and specifically indicates that any modifications to the research must be communicated to the U-M PI and approved by the IRB before implementation (See OM Part 5, Section V for information about unaffiliated investigators).

When reviewing these studies, IRBs should consider whether the community members are provided with sufficient training to perform the research functions and whether there is a clear communication plan between the community members and the PI to convey information about the conduct of the study as well as any adverse events or unanticipated problems that may have been encountered.

When community members are both study team members and research participants, IRBs should examine the study protocol and informed consent materials to ensure that there is a clear delineation between each role, attendant

expectations and risks, and whether community members have been provided with sufficient information to understand the voluntary nature of each role. IRBs should ensure that community members in this dual role have been provided the contact information for the IRB in order to ask questions about their rights as a study team member and/or a research participant to protect them from coercion and undue influence and ensure research integrity.

PART 6: Roles and Responsibilities of Researchers and Research Staff

Describes the roles and responsibilities of researchers and research staff engaged in University research.

I. ELIGIBILITY TO PERFORM RESEARCH AT THE UNIVERSITY OF MICHIGAN

Eligibility requirements for conducting research involving research participants vary depending on the role of the researcher. Engaged study team members must be appropriately qualified by training and/or experience to perform their research responsibilities, and must be listed on the IRB application. See Part 5 of this OM for additional examples of research-related activities considered to constitute "engagement" in research.

A. Principal Investigator

The PI bears ultimate responsibility for all activities associated with the conduct of a research project, including compliance with federal, state and local laws, institutional policies, and ethical principles. The PI remains ultimately responsible even when some aspects of the research are delegated to other members of the study team.

Students/trainees (ie undergraduate students, graduate students, postdoctoral fellows, and other individuals in programs designed to provide non-independent research experiences) are permitted to serve in the role of PI, but must have a faculty advisor (FA) who shares in the student's/trainee's responsibility for the conduct of the research. Undergraduate students may be permitted to serve in the role of PI on minimal risk studies only.

B. Co-Investigator

Co-Investigators (Co-Is) are a subset of the study team who have special responsibilities on research projects. Co-Is are obligated to ensure that the project is designed and conducted in compliance with applicable laws and regulations and institutional policy governing the conduct of research involving research participants. A Co-I must be qualified by training and experience to conduct his or her responsibilities on the research project.

Each Co-I must explicitly acknowledge to the IRB their participation as a Co-Investigator on the study and will be asked to acknowledge their addition to any existing IRB-approved study. Co-Is will be notified of, but will not be required to acknowledge, submissions from the PI to the IRB, such as amendments, adverse event reports, scheduled continuation reviews, and terminations, and any related communications regarding such submissions.

C. Subinvestigator

"Subinvestigator" is a term specific to FDA-regulated studies. It identifies study team members who perform critical clinical trial-related procedures and/or make important trial-related decisions. Generally, these are also study Co-Is, but other study team members with critical and important trial-related roles may serve as Subinvestigators. The term "Subinvestigator" is not used in the U-M IRB application.

D. Faculty Advisor

All research conducted by students/trainees, including postdoctoral fellows, must include a FA as a member of the study team. In addition to the expectation that the FA provide active mentorship to the trainee during the conduct of the research, the FA shares responsibility with the student/trainee researcher for the ethical and regulatory compliance conduct of the research and is institutionally accountable for the study.

E. Other Study Team Members

Other study team members include individuals who contribute to the scientific development or execution of a study in a substantive, measurable way, and include:

- Study Coordinator: The Study Coordinator is a research professional that works under the direction of the PI to support, facilitate and coordinate the daily study activities and plays a critical role in the conduct of the study.
- Administrative Staff: Individuals who are not involved in the design, conduct, or reporting of research (e.g. unit administrators). These individuals are not required to accept their role or complete conflict of interest questions.
- Research Staff: Individuals who are involved in the design, conduct, or reporting of research. These individuals must accept their role and answer conflict of interest questions prior to IRB submission of the application.
- Biostatistician: Statisticians are study staff that analyze data collected during the study.
- Consultant: A consultant is a specialist in a specific area of the study, usually from outside the normal study staff.
- Other: If the study team member doesn't fit into any of the above categories, you can select "Other" and then enter the role of the study team member.

F. Students/Trainees

U-M students/trainees serve as PIs, however supervision by faculty members is required for any research performed by students/trainees in any role, to ensure the proper conduct of research and protection of participant rights and welfare.

Table 7 provides information about permissible roles for U-M faculty, students/trainees, and staff on IRB applications. Exceptions to these requirements are at the discretion of the IO or designee.

Table 7: Who May Serve as PI, Co-I/Subinvestigator, or Faculty Advisor/Mentor on IRB Applications

Current Status	PI	Co-I / Subinvestigator	Faculty Advisor / Mentor	Additional Requirement(s) (non-exempt human research)
Instructional Faculty Research Faculty Clinical Faculty Active Emeritus Faculty Librarian Curator Archivist	Yes	Yes	Yes	None
Adjunct Faculty Visiting Faculty Lecturer Instructor	Yes	Yes	No	• Application includes Faculty Advisor/Mentor, OR

Current Status	PI	Co-I / Subinvestigator	Faculty Advisor / Mentor	Additional Requirement(s) (non-exempt human research)
				• Documented participation on a sponsored project (PAF), OR • Other documented permission of the unit
Staff	Yes	Yes	No	• Documented participation on a sponsored project (PAF), OR • Other documented permission of the unit or as required as part of their U-M job responsibilities
Student Trainees: • Undergraduate Students (minimal risk studies only) • Graduate Students • Professional Degree Students • Residents/Interns/House Officers • Clinical Fellows • Postdoctoral Fellows ○	Yes	Yes	No	Application must include Faculty Advisor/Mentor (exempt and non-exempt human subjects research)
Other qualified individuals	No	Yes	No	Permission of the IRB

II. ROLES AND RESPONSIBILITIES OF RESEARCHERS AND RESEARCH STAFF FOR THE PROTECTION OF RESEARCH PARTICIPANTS

A. Key Responsibilities for Principal Investigators

The PI has primary responsibility for protecting the rights and welfare of research participants in research. Details about the HRPP general requirements for protecting research participants are provided in Part 7 of this OM. The PI's

primary responsibilities also include the following:

1. Delegation of Responsibilities
PIs must personally perform or delegate to qualified Co-Is or research staff all of the necessary tasks to carry out their studies. Even when specific tasks are delegated, the PI remains ultimately responsible for proper conduct of the study and fulfillment of all associated obligations.

2. Oversight of the Research Team
The PI must provide members of the research team with sufficient oversight, training and information to facilitate appropriate safety procedures and protocol adherence. In addition, the IRB must be informed if a PI is no longer able to fulfill his or her duties for any reason, but not limited to, traveling for a prolonged period of time. (Note: any absence longer than three months must be reported to the IRB).

3. Knowledge of Human Research Protection Standards
The PI, Co-Is, and study team members (together referred to as "researchers" or the "study team") are expected to be knowledgeable about and comply with the requirements of each of the following:

- The Common Rule and other federal research laws and regulations;
- Applicable state law;
- The University's Federalwide Assurance;
- Institutional policies and procedures for the protection of research participants and reporting and managing conflicts of interest;
- Requirements of the U-M and non-U-M IRBs reviewing the research;
- The terms and conditions of any research agreements (with government or private sponsors); and
- The basic ethical principles that guide human research.

Some of the laws and regulations that most directly and routinely impact the conduct of human participant research studies are described in Part 11 of this OM. Institutional policies and procedures include this OM, as well as policies and procedures maintained by the academic units to which researchers and research staff are appointed, IRB policies and procedures, and the policies and procedures of other research review units with relevant oversight responsibilities, such as the Research Pharmacy and Radiation Safety Services.

4. Evaluation of Adequacy of Resources
PIs must ensure that adequate resources (facilities, equipment, supplies, and personnel) exist to:

- Conduct the research (eg through internal or external funding for staff, facilities and equipment);
- Protect participants; and
- Ensure the integrity of the research.

Researchers responsible for multi-site research should evaluate the resources available at each site where the research will be conducted.

5. Training Requirements
Researchers must complete educational training as required by the University, the relevant IRB, Sponsor, and other review units prior to initiating research, and should not undertake responsibility for human research studies unless they understand these requirements and are willing to be held accountable for complying with the relevant standards and protecting the rights and welfare of research participants. For additional information on training for human research refer to Part 13 of this OM.

B. Key Responsibilities for Researchers

Following are descriptions of some of a researcher's central obligations when conducting studies involving research participants. They are intended only as a general guide and do not contain a comprehensive description of all researcher responsibilities.

1. Minimizing Risks to Participants and Protecting Participant Rights and Welfare

Federal regulations, institutional policy, and guiding ethical standards require that human research be designed to minimize risks to participants. Minimizing risks and protecting research participants take precedence over the goals and other requirements of any research endeavor.

Study Design

One of the ethical justifications for research involving research participants is the social value of advancing scientific understanding and promoting human welfare. However, the value of research depends upon the integrity of study results. If a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put participants at risk or even to inconvenience them through participation in such a study.

To minimize risks to participants and protect participants' rights and welfare:

- Researchers are expected to design protocols that comply, at a minimum, with applicable regulatory and institutional policy requirements, as well as the principles of the Belmont Report (ie respect for persons, beneficence, justice);
- The research must be reasonably expected to answer its proposed question; and
- The knowledge reasonably expected to result from the research must be sufficiently important to justify the undertaking.

All research procedures must be consistent with sound research design. For example:

- Recruitment and enrollment plans should promote equitable participant selection (ie participants should equitably bear the burdens and enjoy the benefits of participation in research);
- Whenever appropriate, researchers should use procedures already being performed on participants for diagnostic and treatment purposes;
- When appropriate, research plans should make adequate provision for (a) monitoring participants to promptly detect any adverse events and (b) reviewing data collected to ensure participant safety;
- Research plans must contain adequate provisions to protect the privacy of participants and maintain the confidentiality of data collected;
- If some or all of the participants in a study are likely to be vulnerable to coercion or undue influence (eg children, prisoners, cognitively impaired adults, or economically or educationally disadvantaged people), the research plan should provide for additional safeguards, as appropriate, to protect their rights and welfare. For additional information on protections for vulnerable participants refer to Part 7 of this OM.

2. Obtaining and Documenting Informed Consent

a. Informed Consent Required Before Research Participation

Informed consent must be obtained from and documented for each prospective research participant (or their legally authorized representative) for all non-exempt human research before they begin to participate in the research (including any related eligibility testing not conducted solely for clinical purposes), unless the appropriate IRB has approved a waiver or alteration of consent, or waiver of documentation, as described

in Part 3 of this OM. 45 CFR 46.116(a) provides the general requirements of informed consent.

b. Informed Consent Is an On-Going Process

Informed consent is not a single event or document, but an ongoing process that takes place between the PI (or other key personnel, as appropriate) and the research participant. Informed consent requires full disclosure of the nature of the research and the participant's involvement, adequate understanding on the part of the participant (or their legally authorized representative), and the participant's voluntary decision to participate. "The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information." (45 CFR 46.116(4))

c. Responsibility for Obtaining Informed Consent

The PI is responsible for ensuring that each potential participant understands the nature of the research and participation in the project and gives his or her, or their legally authorized representative, informed consent to participate. Although the PI may delegate responsibility for part or all of the consent process to co-Is or research staff, the PI remains responsible for ensuring each participant has been properly consented; and must provide a description of the consenting process to the IRB, including any waiting period between informing the prospective participant and obtaining consent as applicable. If the PI contracts with a firm to obtain consent, the firm must have its own IRB approval, or be covered under the PI's IRB approval.

d. Elements of Informed Consent

The OHRP outlines the information (Informed Consent Checklist) that must be conveyed to participants as part of the informed consent document and process (45 CFR 46.116).

General Requirement - Key Information Section

Informed consent "must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension." (45 CFR46.116(a)(5)(i))

Required Basic Elements

The informed consent document must contain at least the basic elements as listed below:

1. A statement that the study involves research
   This includes explaining the purposes of the research and any procedures that the participant will undergo and specifying which procedures are experimental (eg a new drug, extra tests, non-standard methods of management such as randomizing the participant to a treatment or placebo arm). The statement must describe how much time the participant can expect to devote to the study (eg how long will study visits or research-related procedures take, what is the total expected length of participation after enrollment).

2. A description of any reasonably foreseeable risks
   This includes any reasonably foreseeable risks, discomforts, inconveniences, and harms associated with the research activities. These risks should neither be understated nor glossed over. If additional risks are identified during the course of the research project, the IRB must be informed. In such cases, the IRB may require revisions to the consent process and document(s), and may require participants previously consented to be re-contacted and informed about the new risks. The IRB must approve any protocol or consent revisions and any proposed communication to participants about these revisions.

3. A description of any benefits to the subject
   Subjects must be provided with information about any benefits that may reasonably be expected from the research, either to them individually or to society at large. If there is no reasonable expectation of direct benefit, the subject must be informed. Payments for participation may never be listed as benefits of the research.

4. A disclosure of appropriate alternative treatment
   To ensure participants can make an informed choice about participation in therapeutic research, appropriate alternatives to the study's therapeutic benefits must be described, where applicable. Researchers should be reasonably specific in describing the nature and type of available alternatives.

5. A statement describing the protections to privacy and confidentiality
   Participants must be told the extent, if any, to which individual privacy and confidentiality of research records that may identify them will be maintained, and who will have access to those records. For example, sponsors, funding agencies, regulatory agencies, and IRBs and other institutional officials may review research records. Depending on the nature and scope of the study, other regulations may apply, in addition to the Common Rule, such as HIPAA for studies that involve the collection, use, or disclosure of protected health information.

6. For research involving more than minimal risk, a statement addressing research related injury
   For research involving more than minimal risk, the consent process must provide an explanation as to whether any compensation or treatment will be provided to an injured participant (injury in this context refers both to physical injuries and to less tangible injuries, such as injury to reputation or legal rights). If so, the compensation and treatment should be described, or the participant should be told where to find additional information. In no event may the consent process or the documentation of consent include exculpatory language (eg requiring participants to give up legal rights to which they otherwise would be entitled, such as the right to sue in case of an adverse response to a study intervention). Additional information on medical care for research-related injury for sponsored projects is described in Part 10 of this OM.

7. An explanation of whom to contact for questions or concerns
   Participants must be informed about whom to contact for answers to pertinent questions or concerns about the research or their rights as research participants, as well as whom to contact in the event of a research-related injury, if injuries are foreseeable. Specifically, they should be told how to contact the researchers and whom they can contact if they cannot reach or do not want to speak with the researchers. They also should be told how to lodge a complaint (eg by contacting the IRB office or the HRPP Director, or, in the case of a privacy concern, the Privacy Official). Participants may file an anonymous complaint using the University's Compliance Hotline.

8. A statement that participation is voluntary
   Participants must be specifically informed that participation in a project is on a voluntary basis; that they may discontinue participation at any time; and that no penalty will be imposed, and no rights to which they would otherwise be entitled be waived as a result of refusal to participate in the research or later withdrawing from the research.

9. One of the following statements about the collection of identifiable private information or identifiable biospecimens, as applicable:

a) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after removal, the information or biospecimens could be used for future research studies or distributed to another researcher for future research studies without additional informed consent from the participant or the legally authorized representative, if this might be a possibility; or

b) A statement that the participant'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.

e. Additional Elements of Informed Consent

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

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

2. Anticipated circumstances under which the participant 's participation may be terminated by the researcher without regard to the participant 's or the legally authorized representative's consent;

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

4. The consequences of a participant 's decision to withdraw from the research and procedures for orderly termination of participation by the participant;

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

6. The approximate number of participants involved in the study;

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

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

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

Additional requirements that apply to FDA regulated research are listed in section II.C of this part.

Note: U-M has not implemented “broad consent” for storage, maintenance, and secondary research with identifiable private information or identifiable biospecimens (collected either for research studies other than the proposed research or non-research purposes) and therefore regulatory requirements per 45 CFR 46.116(d) are not applicable.

f. Other Consent Requirements

- The consent form should not release or appear to release the researcher, sponsor, institution, or its agents from liability for negligence.

- The consent form should include the amount and schedule of all payments to the participant.
- For FDA-regulated research, the consent form should include a statement that notes the possibility that the FDA may inspect the records, and that the results of the research will be posted on Clinicaltrials.gov, if applicable.
- The consent form must be approved in advance by the IRB.
- The consent form will be signed by the participant or their legally authorized representative.
- In some cases, the IRB may approve a waiver or alteration of consent, or waiver of documentation, as permitted by federal regulations and as described in Part 3 of this OM. A waiver of documentation means that the potential participant is provided all of the information required for informed consent, but is not asked to sign a consent form.
- Oral or written information must be conveyed in language that is understandable to the participant or their legally authorized representative.
- Researchers must ensure that consent is sought only under circumstances that minimize the possibility of coercion or undue influence. For example, participants must be given a sufficient opportunity to determine whether or not to participate in the study. It is therefore desirable to allow time between the initial discussion of the opportunity to participate in the research and the final decision, as recorded in the consent document.
- Each participant (or their legally authorized representative) must be provided with a copy of the consent document at the time of consent, unless the IRB specifically has waived this requirement. If the study is using or disclosing PHI, the participant must be provided a copy of the signed document, per HIPAA regulations, otherwise, this need not be a signed copy.

g. Short Form Consent Process

In limited circumstances, (eg for illiterate or non-English speaking participants), the IRB may approve the use of a "short form" consent process. In the "short form" consent process, the required elements of informed consent normally presented in writing are presented orally to the participant or participant's legally authorized representative in the presence of a witness (45 CFR 46.117(b)(2)).

Requirements for using "short form" consent:

- The IRB must approve a written summary of what is to be said to the participant or representative and ensure that it includes the elements of informed consent required by HHS and/or FDA regulations;
- An independent witness must be present at the oral presentation;
- The participant or their legally authorized representative signs only the short form itself;
- The witness must sign both the short form and a copy of the written summary;
- The person obtaining consent must sign a copy of the written summary;
- Copies of both the short form and the written summary must be provided to the participant or their legally authorized representative;
- For participants who do not speak English, the witness must be conversant in both English and the language of the participant.

h. Retention of Signed Consent Document

Signed consent documents must be retained for:

- At least three years after completion of the research (seven years if protected health information will be used or disclosed in connection with the study in accordance with HIPAA requirements); or
- Longer if required by institutional policy or applicable sponsor agreements or regulations.

A copy of the complete signed consent should be placed in the medical record of participants, particularly

when the research intervention may affect other treatment or care. Depending on the circumstances of the study, they may also be required to maintain documentation of HIPAA-compliant authorization.

3. Compliance with IRB and Other Requirements

An IRB must review and approve all research activities that meet the definition of human research before they are initiated, unless an IRB has determined that the activities are exempt from IRB oversight (see Part 4 of this OM for additional details). Prior IRB approval is also required for pre-research activities such as access to databases containing private information and screening data for possible recruitment and enrollment. IRB approval for such activities is necessary, but not sufficient; the PI must also comply with other policies, at the University or otherwise, governing access to such databases. For example, access to a U-M database would typically require permission of the University data steward as well as the creation of a Memorandum of Understanding setting forth the terms and conditions applicable to use of that database for approved research purposes.

When applicable, the IRB is also responsible for review and approval of continuing review (see Part 3 of this OM for information on continuing review requirements), progress reports, change of protocol, adverse event reporting, ORIO reporting, monitoring and record keeping. Researchers must at all times cooperate with the IRB in fulfilling its responsibilities.

PI Obligations

1. IRB Submissions

The PI is responsible for the content of all submissions (eg initial review, continuing review, adverse event reporting, ORIO reporting) to the IRB and other review units and for ensuring that those documents are submitted in a timely manner, as required by the IRB or other review unit. The PI must include on the IRB application all study team members who contribute to the scientific development or execution of a study in a substantive, measurable way. Multi-site studies relying upon a U-M IRB as the IRB-of-Record must develop procedures to assure timely communication of information in association with these reporting requirements.

2. Responding to IRB Requests for Information

To assist the IRB in fulfilling its responsibilities, researchers must provide all information requested by the IRB in a timely fashion.

3. Adhering to Approved Protocol

Researchers must conduct research as specified in the IRB-approved protocol and must comply with all IRB determinations, including directives to terminate participation in designated research activities.

4. Changes to Research

Any proposed changes in the research must be submitted to the IRB via an amendment application and approved *in advance* by the IRB unless necessary to eliminate apparent immediate hazards to participants. Similar requirements apply for other review units (eg Research Pharmacy, Radiation Safety Services, etc.*)* responsible for oversight of research activities. Researchers must promptly report to the IRB any additional risks that are identified during the course of the research project.

5. Continuing Review (when required by the IRB)

PIs are responsible for monitoring their approval periods and submitting a continuing review application in a timely manner so as to permit the IRB to review and issue an approval prior to expiration of the study's previous approval.

6. Lapse of IRB Approval

If IRB approval for a study lapses for any reason, even if the researcher submitted an application for review in a timely manner and promptly responded to any requests for clarifications or changes, the research must stop until the IRB issues its formal approval or determines that it is in the best interest of individual participants to continue participating in the research interventions or interactions.

7. Reporting to the IRB

Researchers must promptly report to the IRB any of the following:

- Unanticipated problems involving risks to participants or others, such as an adverse event or exposure of a member of the research team to a harmful substance;
- Potential noncompliance with applicable laws or regulations or IRB requirements, whether by researchers, research staff, or others, even if the noncompliance was unintentional or was discovered in the course of quality assurance or quality improvement activities; and
- Disapprovals, suspensions, or terminations of the project by any University or non-University review units or agencies (eg the Research Pharmacy or IBC, or the IRB at another performance site, or a regulatory agency such as the NIH, FDA, or National Science Foundation (NSF)).

Part 12 of this OM provides additional details on reportable events.

8. Audits and Inspections

Researchers and research staff are expected to cooperate with:

- Internal evaluations, inspections, and audits performed by authorized internal oversight authorities, including the IRBs, the Office of Research Compliance Review (ORCR) and the Office of University Audits; and
- External reviews (eg by government agencies such as the FDA or NIH Office of Research Integrity). Any external investigation, inspection, or other external review and its outcome must be reported to the IRB responsible for the research in question upon receiving notice. Researchers should consult with their administrators, the IRBs, as appropriate, the UMOR, and/or the Office of the Vice President and General Counsel for assistance and representation.

4. Conflict of Interest

Outside interests relating to human research must be disclosed in both the University's outside interest disclosure system known as M-Inform and in eResearch forms (eg HUMs, PAFs).. Such interests are not inherently wrong, even when they create a conflict of interest, as long as they are disclosed and appropriately managed or resolved. A conflict of interest may arise when a faculty or staff member has a relationship with an outside organization that puts the faculty or staff member in a position to influence the university's decisions in ways that could lead directly or indirectly to financial gain for the faculty or staff member or his or her family, or give improper advantage to others to the detriment of the University.

The University and individual academic units have established mechanisms to identify and manage potential conflicts, including annual disclosure requirements, research and sponsored project application questions, and informal communications. In addition, when a U-M IRB agrees to be the IRB-of-Record for multi-site research, each site must provide information to the reviewing IRB about any potential COI situations disclosed by non-U-M individuals involved in the research, including any existing management plans. For detailed information about the University's conflict of interest and commitment policies, see the Conflict of Interest Policies website.

A researcher who believes he or she or other members of the research team may have a related interest or conflict that has not otherwise been disclosed should consult with the appropriate conflict of interest committee for guidance to determine whether the conflict is reportable and, if so, how it might be managed (see Part 9 of this OM for additional guidance).

5. ClinicalTrials.gov Registration and Results Reporting

Certain clinical studies involving research participants must be registered on and have results posted in ClinicalTrials.gov. For a full description of ClinicalTrials.gov requirements, refer to Part 11 of this OM.

6. Clinical Trial Informed Consent Posting

One IRB-approved consent form used to enroll participants, for each federally-funded clinical trial must be posted on a publicly available federal website, as specified by the US Federal government. See Clinical Trial Informed Consent Form Posting (45 CFR 46.116(h)).

- The PI or designee is responsible for posting the consent form;
- The consent form must be posted on the website after the clinical trial is closed to recruitment, but no later than 60 days after the last study visit by any participant, as required by the protocol; and
- Any requests to redact certain information prior to posting must be submitted to the Federal department or agency supporting the clinical trial prior to posting.

C. Studies Regulated by the Food and Drug Administration

When conducting research involving FDA-regulated products, researchers must comply with all applicable FDA regulations and fulfill all investigator responsibilities or all sponsor-investigator responsibilities, as applicable. Refer to Part 8 of this OM for a description of the circumstances under which human research becomes subject to FDA regulations. In addition to requirements outlined in this part and in Part 8, the following data access and retention requirements apply:

- When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having the data removed;
- A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as laboratory results obtained through chart review, and addresses the maintenance of privacy and confidentiality of the participant's information;
- Using an IRB-approved consent document, the researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document); and
- If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

D. Other

PIs have additional responsibilities when studies are required to follow guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH GCP). Guidance on ICH GCP is included in Part 11 of this OM.
PIs may have additional responsibilities for federally sponsored research based on the department providing support

(eg DOD, Department of Education, etc.) See guidance documents at HRPP Guidance for Federally Sponsored Research.

PART 7: Participant Protection

Describes some of the ways research participants are protected under the HRPP, including:

- Special protections for vulnerable participants;
- Requirements for Data and Safety Monitoring Plans and Boards;
- Review of advertising and recruitment materials;
- Payment to research participants; and
- Compensation for injuries.

I. HRPP PROTECTION EXTENDS TO ALL PARTICIPANTS

The HRPP protects the rights and welfare of all individuals who participate in University research as research participants, regardless of whether they are intended "primary" participants of the research or their participation is ancillary to the main study intervention. For example, a survey might ask primary participants for private information about their friends or family members. If that information is identifiable those friends and family members are considered research participants in addition to the primary participant. See Part 4, II of this OM for a definition of human subjects.

The classification of certain individuals or groups of individuals as human research participants or not human research participants is important because it triggers a number of requirements under federal regulations and the HRPP.

II. VULNERABLE PARTICIPANTS

Additional protections are required when vulnerable participants participate in research. Federal regulations identify pregnant women, fetuses, neonates, children, and prisoners as vulnerable participants (45 CFR 46, Subparts B, C, D). IRBs and researchers must consider if some or all participants in a protocol are likely to be vulnerable beyond regulatory definitions, and ensure that additional safeguards are in place to protect the rights and welfare of these participants. Vulnerable populations include, but are not limited to:

- Children (individuals who have not attained the legal age to consent for procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted);
- Pregnant women, fetuses, and neonates;
- Prisoners (individuals involuntarily confined or detained in a penal institution, including individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing);
- Individuals who are cognitively impaired or lack decision-making capacity; and
- Individuals who otherwise may be subject to coercion or undue influence (eg economically or educationally disadvantaged persons; employees or students of researchers conducting the study; patients of physician-researchers).

When members of any of these groups participate in research, University IRBs require researchers to specify what additional protections, if any, will be provided to these persons to protect their rights and welfare (eg minimize risks unique to these groups and the possibility of coercion or undue influence). In reviewing these research projects, the IRBs ascertain that inclusion of a vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to that population.

Laws governing research involving vulnerable populations, including laws on who may consent on behalf of children or cognitively impaired or incapacitated adults, vary from state to state. Guidance on Michigan law, additional

requirements of federal funding agencies, and international research is described in Part 11 of this OM.

The University IRBs apply the following standards when reviewing research involving vulnerable populations:

- For federally supported research, the IRBs comply with all of the requirements of 45 CFR 46to the extent the sponsoring agency has adopted the standards reflected in Subparts B-D.
- For FDA regulated research involving children, the IRBs comply with the requirements of 21 CFR 50, Subpart D and 21 CFR 56.
- For research not subject to the above regulations, U-M has developed standards that are intended to provide protections equivalent to those described in federal regulations. In some cases, the IO substitutes to provide judgment normally assigned to the HHS Secretary in certain situations described below.

A. Research Involving Pregnant Women, Fetuses, and Neonates

See 45 CFR 46, Subpart B for additional protections for pregnant women, human fetuses and neonates involved in federally-funded research.

When applying equivalent protections to non-federally funded research involving pregnant women, fetuses and neonates, the following exceptions may apply:

- Research that does not hold out the prospect of direct benefit to the woman or fetus may still be approved as long as (1) the risk presented is no more than minimal and (2) the research is intended to generate generalizable or scientific knowledge. This is different than the requirements of 45 CFR 46.204 and 45 CFR 46.205, which require the research to contribute to the development of important biomedical knowledge.
- Research described as 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 may be approved by the IO or DIO after consultation with a panel of experts in pertinent disciplines. In granting the approval, the IO or the DIO must determine that the research will be conducted in accord with sound ethical principles and informed consent will be obtained in accord with the informed consent standards described in 45 CFR 46, Subpart A.

B. Research Involving Prisoners

See 45 CFR 46, Subpart C for additional protections pertaining to federally-funded research involving prisoners as subjects.

The IRBs follow federal guidance and U-M guidance when a research participant becomes a prisoner during the course of a study.

When applying equivalent protections to non-federally funded research involving prisoners, the following exceptions may apply:

The IO or DIO assumes the role of the HHS Secretary for studies requiring certification or approval as described in 45 CFR 46.306(a)(2). The IRB will certify to the IO or DIO that the research meets the criteria for approval of research with prisoners.

IRB Composition
For research reviewed by the convened IRBs involving prisoners:

- The prisoner representative must be a voting member of the IRB, or an alternative member who becomes a voting member when needed;
- The prisoner representative must review research involving prisoners and receive all materials pertaining to the research (the same as primary reviewers);
- The prisoner representative must be present at a convened meeting (in-person, by phone, video-conference or webinar) when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved;
- 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;
- Substantial modifications to previously approved research reviewed by the convened IRBs must use the same procedures for initial review including the responsibility of the prisoner representative;
- Continuing review done by the convened IRB must use the same procedures used for initial convened review, including the responsibility of the prisoner representative. If the continuing review qualifies for expedited review, it will follow the requirements for expedited review of research involving prisoners that follows below.

Minor modifications to previously approved research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.

Research involving interaction or intervention with prisoners (including obtaining consent) may be reviewed using the expedited procedure if a determination is made that the research poses no more than minimal risk to the prisoners being studied or included and that the research meets the criteria for expedited review. The research must be reviewed by a prisoner representative, either as the expediting reviewer or as a consultant, who must confirm that the research poses no more than minimal risk to the prisoner participants. Review of subsequent modifications and continuing review submissions via expedited procedures must also involve the prisoner representative as a consultant or expediting reviewer.

Research involving prisoners that does not involve interaction or intervention (eg existing data, record review) may be reviewed using the expedited procedure, if a determination is made that the research poses no more than minimal risk to the prisoners being studied or included and the research meets the criteria for expedited review. The prisoner representative may review the research as an expediting reviewer or consultant, but such review is not required. Review of subsequent modifications and continuing review submissions via expedited procedures may involve review by the prisoner representative as a consultant or expediting reviewer, but is not required.

C. Research Involving Children

See 45 CFR 46, Subpart D for additional protections for children involved as subjects in federally-funded research and 21 CFR 50, Subpart D for additional safeguards for children involved in FDA regulated clinical investigations.

When applying equivalent protections to non-federally funded research involving children, the following exceptions may apply:

- The IRB finds and documents that the research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
- Approval is secured from the IO or DIO after consultation with a panel of experts in pertinent disciplines. In granting the approval, the IO or the DIO must determine that the research will be conducted in accord with sound ethical principles and adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians consistent with the standards described in 45 CFR 46.408.

Research involving children requires that adequate provisions are made for soliciting the assent of the child. In limited circumstances, the IRB may determine that assent is not a requirement with respect to some children involved in research for one of the following reasons:

- The capability of the children is so limited (based on an assessment of their age, maturity, or psychological state) that they cannot reasonably be consulted;
- 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 child and is available only in the context of the research; or
- The assent can be waived using the criteria described in 45 CFR 46.116 for waiver of consent.

Children who reach the age of majority while participating in a study must be re-consented if continuing interventions or interactions are planned (including collection or analysis of identifiable private information), as described in 45 CFR 46.116. The IRB may grant a waiver of re-consent under 45 CFR 46.116 (e), if it finds that required conditions are met, but must document its decision and rationale for doing so.

D. Research Involving Adults with Cognitive Impairment or Otherwise Impaired Decision-making Capacity

Cognitive impairment or impaired decision-making capacity covers a broad spectrum of conditions and timeframes. One individual may be severely cognitively impaired from birth, whereas another otherwise healthy person, who is in shock, may be temporarily decisionally impaired. Alternatively, a person with a mental health condition may have fluctuating decision-making capacity.

Federal regulations do not include specific protections for adults with impaired decision-making capacity, as they do for research with pregnant women, prisoners, and children. Through eResearch, however, the IRBs determine whether research involves participants who have diminished decision-making capacity. The IRBs also consider limiting the types of research in which cognitively impaired adults may be enrolled based on the purpose, risk, and potential benefit of the research and whether the research question could be answered by enrolling adults who are able to consent.

In each such identified case, the protocol or application must describe any additional safeguards planned to assure appropriate consent. The IRB then must evaluate the appropriateness of the research and the adequacy of the PI's proposed plan for initial and, if applicable, ongoing assessment of participants' capacity to consent. For those participants unable to consent, the IRB must determine whether assent must be secured and, if so, whether the PI's proposed plan for assent is adequate. The requirement for assent may be waived by the IRB only if:

- The capability of some or all of the participants is so limited that they cannot reasonably be consulted;
- The intervention or procedure holds out the prospect of direct benefit to the health or well-being of the participants and is available only in the context of the research; or
- The research otherwise meets the conditions for waiver of consent consistent with the standards described at 45 CFR 46.116 or 46.117.

An IRB may approve participation of adults with cognitive impairment or diminished decision-making capacity only under the following circumstances:

1. Research Involving No More Than Minimal Risk

Research involving no more than minimal risk may be approved only if the IRB finds and documents that adequate provisions have been made for soliciting assent from the participant, if appropriate, and permission of the participant's LAR (eg next-of-kin or legal guardian). The IRB may approve an exception to the assent requirements if the standards described in 45 CFR 46.408(a) are met. The IRB may approve an exception to the requirement for permission of the participant's LAR if a waiver of consent or documentation of consent would be acceptable under 45 CFR 46.116 or 46.117.

2. Research Involving Greater Than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Participants

Research involving greater than minimal risk may be approved if the IRB finds and documents that:

- The intervention or procedure under investigation holds out the prospect of direct benefit to individual participants, or the monitoring procedure is likely to contribute to the participant's well-being;
- The risk is justified by the anticipated benefit to participants; and
- The relation of the anticipated benefit to the risk is at least as favorable to participants as that presented by available alternative approaches; and adequate provisions have been made for soliciting assent from the participant and permission from the participant's LAR, or assent is waived consistent with the standards described in 45 CFR 46.408(a).

3. Research Presenting as Greater Than Minimal Risk Without the Prospect of Direct Benefit to the Individual Participants

Research involving greater than minimal risk may be approved if the IRB finds and documents that:

- The research presents a minor increase over minimal risk without the prospect of direct benefit to the individual participants, but the research presents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of cognitively impaired adults or adults with diminished decision making capacity; and
- Approval is secured from the IRB in consultation with experts in pertinent disciplines who determine that the research will be conducted consistent with sound ethical principles and that adequate provisions have been made to solicit the assent of the participant and permission of his or her LAR, consistent with the standards described at 45 CFR 46.408(a).

III.DATA AND SAFETY MONITORING PLANS AND BOARDS

Data and safety monitoring is a process designed to protect the safety of individual participants in research studies and to ensure the validity of research results and scientific integrity of a study. The portions of a protocol that describe the steps the research team will take to identify, address and report any physical, social, or psychological events that may result from participation in a study constitute a Data and Safety Monitoring Plan (DSMP). A DSMP typically describes the timing, tools and/or methods to be employed for monitoring and evaluating study data during the course of the project, procedures for treatment or resolution (including a description of circumstances that will result in halting or terminating research), and procedures for and timing of reports to oversight bodies, such as the IRB, an independent monitor, an internal committee, a Data and Safety Monitoring Board (DSMB), the NIH, or the FDA.

University IRBs are required to ensure that, when appropriate, research plans make adequate provision for monitoring data collected to ensure participant safety. DSMPs are submitted as part of the eResearch application and are reviewed as part of the initial review, or are submitted as part of an amendment, and must be approved prior to implementation. The IRB may consider:

- What safety information will be collected, including serious adverse events;
- How the safety information will be collected;
- The frequency of data collection, including when safety data collection starts, and the frequency of review of cumulative data;
- Inclusion of a DSMB, and the plan for reporting findings to the IRB and sponsor;
- For studies that do not have or are not required to have a DSMB and are blinded, multi-site, enroll vulnerable participants, or use high-risk interventions, the IRB carefully reviews the DSMP to determine if a DSMB is needed;

- If applicable, studies not using a DSMB may use statistical tests to analyze safety data to determine if harm is occurring;
- Provisions for the oversight of safety data (eg by a DSMB); and/or
- Conditions that trigger an immediate suspension of research, if applicable.

In some cases, such as NIH sponsored multi-site clinical trials involving risks to participants, DSMBs are required. In other cases, such as high risk research or where institutional or individual conflicts of interest dictate the need for external review mechanisms, a DSMB may be established. A DSMB is a formally chartered, independent committee whose stated goal is to protect the welfare and safety of the participants participating in a specified research study and to promote scientific integrity. For example, DSMBs may be chartered when:

- The study is intended to provide definitive information about the effectiveness and/or safety of a medical intervention;
- Prior work suggests that the intervention under investigation may induce a potentially unacceptable toxicity;
- The study will evaluate mortality, morbidity, or other significant endpoints such that the inferiority of one treatment arm has safety as well as effectiveness implications; and/or
- The study raises ethical issues and it would be important for the study to stop early if the primary scientific question had been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.

On a periodic basis, a DSMB:

- Approves proposed safety measures for a protocol;
- Provides written documentation of protocol review and agreement with study design;
- Reviews study progress as provided in its charter;
- Reviews cumulative data at established intervals to assess safety and efficacy;
- Consults with PIs concerning safety or integrity issues arising during the course of the study; and
- Provides written reports to the PI, IRB and other oversight authorities summarizing its oversight activities (eg results of chart reviews, summaries of consultations with the PI, concerns regarding participant safety, etc.), and any recommendations (eg continuing the study, continuing the study with modifications, suspending the study for interim analysis, or terminating the study).

A DSMB charter should include at least the following elements:

- A detailed description of the membership, including qualifications and experience;
- Roles and responsibilities of the DSMB;
- Authority of the DSMB;
- Timing and purpose of DSMB meetings;
- Procedures for maintaining confidentiality;
- Format, content and frequency of DSMB reports;
- Guidelines outlining the procedure for the PI's interaction with the board and whether the PI may be invited to attend any open sessions;
- Statistical procedures, including monitoring guidelines, used to monitor the identified primary, secondary, and safety outcome variables; and
- Plans for changing the frequency of interim analyses as well as procedures for recommending protocol changes.

DSMB membership generally should include:

- Multidisciplinary representation of at least three individuals, including physicians and scientists from relevant specialties, and a biostatistician;
- Members that have no involvement in the design and/or conduct of the trial;
- Members that have no significant conflicts of interest with the study, whether they are financial, intellectual, professional, or regulatory in nature; and
- An appropriate number of members (beyond three, as necessary) to address the size and complexity of the study.

Not all studies require a DSMB; the PI and responsible IRB should assess the need for one based on the risk level, complexity, and the size of the study.

Additional information on data and safety monitoring is provided in the NIH Policy for Data and Safety Monitoring and the FDA Guidance for the Establishment and Operation of Clinical Trial Data Monitoring Committees.

IV.ADVERTISING AND RECRUITMENT MATERIALS

IRBs review all advertising materials intended to recruit prospective participants. Recruitment materials are submitted as part of the eResearch application and are reviewed as part of the initial review or submitted as part of an amendment and must be approved prior to implementation. As part of its review, the IRB considers:

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

In its review of advertising materials, an IRB should ensure that the materials:

- Do not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent and the protocol;
- Do not include exculpatory language;
- Do not emphasize the payment or the amount to be paid, by such means as larger or bold type; and
- Do not promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation.

Advertisements should be limited to the information needed by prospective participants to determine their eligibility and interest, such as:

- The name and address of the PI or research facility;
- The purpose of the research or the condition under study;
- A summary of the criteria that will be used to determine eligibility for the study;
- A brief list of benefits to participants, if any;
- The time or other commitment required of the participants; and
- The location of the research and the person or office to contact for further information.

When following FDA regulations, IRBs should review advertisements to ensure that they:

- Do not make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling;

- Do not use terms, such as "new treatment," "new medication," or "new drug," without explaining that the test article is investigational; and
- Do not allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Additional information on review of recruiting methods for FDA regulated research can be found in Recruiting Study Subjects: Guidance for Institutional Review Boards and Clinical Investigators.

V. PAYMENT TO RESEARCH PARTICIPANTS

The University recognizes the importance of encouraging individuals to participate in research as research participants and the value of the time, effort, and risk participants contribute to University research efforts. The University permits payments or other consideration to compensate participants for these contributions, as long as the following criteria are met:

- Payment arrangements are specifically approved in advance by the relevant IRB;
- Payments or other consideration provided to participants in return for their participation are not so significant as to be coercive or unduly influential (eg inducing participants to accept unreasonable risks);
- Payments are prorated when appropriate, and should not be contingent upon the participant completing the study, to avoid inducing participants to continue in a study when they otherwise would withdraw;
- Arrangements are made by the PI to assure proper accounting of payments made to participants, and required reporting to tax authorities, as required by University policy, with due consideration of privacy concerns.

Note: See Standard Practice Guide 501.07, Research Subject Incentives.

VI.COMPENSATION FOR INJURIES

University policy and IRB procedures, as directed under, 45 CFR 46.116(b)(6) require that for research involving more than minimal risk, the informed consent process provide an explanation as to whether any compensation or treatment will be provided to an injured participant (injury in this context refers both to physical injuries and to less tangible injuries, such as injury to reputation or legal rights). If so, the compensation and treatment is described, or the participant is told where to find additional information. Exculpatory language (eg language that provides that a participant "assumes the risk" for participation in a study) is prohibited in informed consent documents.

Part 10 of this OM describes compensation for injuries in relation to sponsored research. Also, OHRP provides additional guidance regarding the use of exculpatory and non-exculpatory language in the informed consent process.

PART 8: Studies Regulated by the FDA and Use of Investigational Articles

I. INTRODUCTION AND DEFINITIONS

The FDA enforces the FD&C Act and other laws and regulations governing the use of drugs, biologics, and devices both in research studies and for treatment.

The FD&C Act generally prohibits the manufacture, delivery, use, receipt, or sale of any drug, biologic, or device that is "adulterated" or "misbranded". New drugs, biologics, and devices that are not yet FDA-approved, as well as those used for a purpose or in a manner not already approved by the FDA, may be considered either adulterated or misbranded, or both.

The FDA has adopted regulations to implement the FD&C Act. FDA regulations for drugs are outlined in 21 CFR 312, and devices are in 21 CFR 812. FDA regulations for informed consent (21 CFR 50) and Institutional Review Boards (21 CFR 56) also apply. Reporting of adverse events and unanticipated problems related to research on FDA-regulated products is covered in IRBMED Standard Operating Procedures and IRBMED Guidance.

The following sections describe when or under what circumstances an IND application, or an IDE is needed (Sections II-VI) and describe the roles and responsibilities of the FDA, IRBs, sponsors, and investigators with respect to protocols involving investigational articles (Sections VII and VIII).

Table 8: Definitions of FDA regulated research.

TERM	DEFINITION
Biological Product	A diverse category of products that are generally large complex molecules that are produced through biotechnology in a living system. For example: blood, blood products, vaccines, allergenics, tissue, and tissue products.
Clinical Investigation	Any experiment that involves a test article and one or more human subjects.
Device	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or intended to affect the structure or any function of the body; AND which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.
In Vitro Diagnostic	An IVD is a medical device. While most other devices function on or in a

TERM	DEFINITION
Device (IVD)	human body, IVDs include products used to collect specimens, or to prepare or examine specimens (eg blood, serum, urine, spinal fluid, tissue samples) after they are removed from the human body.
Drug	A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. A substance (other than food) intended to affect the structure of any function of the body.
Investigator	An individual who actually conducts a clinical investigation (ie under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.
Mobile Medical Applications (Apps)	Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.
Test Article	Any drug, biological product, medical device, electronic product, or other product regulated by the FDA.
Sponsor	A sponsor is an organization or individual that initiates and takes responsibility for a clinical trial or other FDA-regulated project involving a drug, biologic or device.
Sponsor-Investigator	A sponsor-investigator is an individual who both initiates and conducts an investigation of an FDA-regulated drug, biologic or device and under whose immediate direction the drug, biologic or device is administered or dispensed. The term does not include any person other than an individual.

II. RESEARCH INVOLVING INDs OR IDEs

INDs and IDEs are the mechanism by which the FDA grants investigators special permission to conduct research using (1) a new (not yet FDA-approved) drug, biologic, or device, or (2) an FDA-approved drug, biologic, or device for a purpose or in a manner not already approved or cleared for use by the FDA.

Investigators are responsible for determining whether research in which they are engaged requires an IND or IDE and, if so, for securing the necessary FDA permissions and IRB approvals. An investigator who holds an IND or IDE is considered an FDA "sponsor" and must meet FDA sponsor requirements described in Section VII of this part. An investigator who is unsure whether an IND or IDE is required for a proposed research project should consult with the Medical School Institutional Review Board (IRBMED), the Michigan Institute for Clinical and Health Research Investigator IND/IDE Assistance Program (MICHR MIAP), the U-M Research Pharmacy and/or the Office of General Counsel (OGC). Guidance aids available on the IRBMED website summarize the circumstances under which an IND or IDE may be required.
Investigators who fail to obtain an IND or IDE when required by FDA regulations may be subject to University disciplinary actions, FDA disqualification, and to civil and even criminal sanctions.

A. IND Requirements for Research Involving an Investigational Drug or Biologic

An IND is the FDA regulatory mechanism that allows a sponsor to ship an unapproved drug or biologic to study sites and initiate clinical research involving the drug or biologic. IND regulations are outlined in 21 CFR 312.

An IND application is required for testing the safety and/or the effectiveness of:

- Unapproved drugs or biologics;
- Approved drugs or biologics for new intended uses;
- or studies that involve a route of administration or dosage level or use in a patient population that significantly increases the risks associated with the use of the drug product.

Human research involving unapproved drugs and biologics or FDA-approved drugs and biologics for new intended uses may proceed only under an IND that is approved by the FDA before the research begins. The FDA assigns an IND number and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk.

1. Exemptions from IND Requirements

Certain investigations may be exempt from the requirement for an IND, if specified criteria are met. FDA exemption criteria are described in 21 CFR 312.2(b)(1). Investigations that are exempt from IND regulations still require IRB review and approval.
Additionally, a limited number of specific types of clinical investigations (eg involving in vitro diagnostic biologicals such as blood grouping serum, reagent red blood cells, and anti-human globulin) conducted under certain conditions are also exempt from the IND requirement. See 21 CFR 312.2(b)(2)-(6).
Separate rules for bioavailability studies are described at 21 CFR 320.31.

2. FDA guidance regarding IND requirements and exemptions

- Investigational New Drug (IND) Application
- Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND - Guidance for Clinical Investigators, Sponsors, and IRBs

B. IDE Requirements for Research Involving Investigational Devices

An IDE is the FDA regulatory mechanism which permits an investigational device to be shipped lawfully for the purpose of conducting investigations involving that device. IDE requirements are outlined in 21 CFR 812. The FDA assigns an IDE number to a significant risk device and allows the investigation to begin after it determines that research participants will not be exposed to unreasonable risk.

IDE regulations require research investigations to test the safety and/or the effectiveness of the following

investigational devices:

- Unapproved devices;
- Approved devices for new indications.

1. Level of FDA Oversight

The level of FDA oversight of research varies according to the level of risk (significant or non-significant) to research participants posed by the device. IDE regulations, 21 CFR 812, describe three types of device studies:

- Significant Risk Device Studies
- Non-Significant Risk Device Studies
- IDE Exempt Studies

Investigators conducting studies involving medical devices must provide the IRB with complete and accurate information about the regulatory status and risk level of each device.

a. Significant Risk (SR)/Non-significant Risk (NSR) Definition

A SR device is an investigational device that presents a potential for serious risk to the health, safety, or welfare of a subject, and is one of the following:

- Is intended as an implant;
- Is for use in supporting or sustaining human life;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

SR device studies are subject to all of the requirements of 21 CFR Part 812. An IDE application must be approved by the FDA and have IRB approval before the study can begin.

b. Non-Significant Risk Device Studies

A NSR device is an investigational device that does not meet the definition of a significant risk device. A NSR study does not require submission of an IDE application to the FDA. Instead, the sponsor must conduct the study as required by "abbreviated" IDE requirements as outlined in 21 CFR 812.2(b). The "abbreviated" IDE requirements include, among other items, requirements for IRB approval and informed consent, record keeping, labeling, study monitoring, and prohibition against promotion. Unless the sponsor is notified otherwise by the FDA, a NSR study is considered to have an approved IDE if the sponsor fulfills these abbreviated requirements, and the study may begin immediately following final IRB approval.

c. Significant Risk/Non-Significant Risk (SR/NSR) Determination for Investigational Devices

The SR/NSR determination is made initially by the FDA-recognized sponsor (or sponsor-investigator) but must be confirmed by an IRB. IRBs do not have to make the SR or NSR determination if the FDA has already made the risk determination. An FDA guidance document helps sponsors, investigators and IRBs distinguish significant from non-significant risk studies. See Significant Risk and Non-Significant Risk Medical Device Studies - Guidance For IRBs, Clinical Investigators, and Sponsors.

d. Investigational IVDs

While many investigational IVDs are IDE exempt, investigational IVDs used in clinical investigations of therapeutic products may pose significant risk to subjects if the information generated by the use of the investigational IVD affects important aspects of the treatment for the enrolled subjects and, by doing so, directly influences the types of therapeutic products or therapeutic management strategies the subject may

be exposed to during the study. See Investigational IVDs Used in Clinical Investigations of Therapeutic Products - Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards.

e. Mobile Medical Apps

Some mobile medical apps are subject to FDA regulations. The FDA will apply the same risk-based approach the agency uses to assure safety and effectiveness for other medical devices. Additional information about these apps can be found in the FDA guidance document Mobile Medical Applications – Guidance for Industry and Food and Drug Administration Staff. In addition, many mobile applications have Terms of Service, or User Agreements, that researchers need to be aware of and consider when utilizing mobile applications in research.

2. Sponsor's Role

If the sponsor believes the device is NSR, the sponsor provides the reviewing IRB with an explanation of its determination and any other information that may assist the IRB in evaluating the risk level of the device. This includes, at a minimum, the following information:

- A description of the device;
- Reports of all prior investigations with the device (clinical, animal, and laboratory testing);
- The proposed investigational plan;
- A description of patient selection criteria;
- A description of monitoring procedures;
- FDA's assessment of the device study's risk, if one has been made;
- Whether other IRBs have reviewed the proposed study;
- Any other information that the IRB deems necessary to make its decision.

3. IRB's Role

The IRB may agree or disagree with the sponsor's initial assessment. If the IRB agrees with a NSR assessment and approves the study, the study may begin without submission of an IDE application to the FDA. If the IRB disagrees, the sponsor must notify the FDA within five days that a SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The IRB's SR/NSR determination must be based on the proposed use of the device in an investigation and not on the device alone. In making its determination, the IRB must consider the nature of the harm that may result from use of the device. If the harm could be life-threatening, result in permanent impairment, or necessitate medical or surgical intervention to preclude permanent impairment, the device must be treated as SR. If the subject must undergo a procedure as part of the study (eg surgery), the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm that could be caused by the device. In making its SR/NSR determination, the IRB may consult directly with the FDA for its opinion.

4. FDA's Role

The FDA has the ultimate authority to determine whether a device study is SR or NSR. In the event that the FDA becomes aware of, and disagrees with, an IRB's NSR determination, an IDE application must be submitted to the FDA. Conversely, if a sponsor files an IDE with the FDA because the study is presumed to be SR, but the FDA classifies the study as NSR, the FDA will return the IDE application to the sponsor and the study may be presented to IRB(s) as a NSR investigation.

Once a final SR/NSR decision is made by the IRB (or the FDA), the IRB must consider whether the study should be approved, using the same criteria it would use in reviewing any other research involving FDA-regulated products.

A sponsor shall not begin an investigation for which the FDA's approval of an application is required until an IRB and the FDA have both approved the study. See 21 CFR 812.20(a)(2) and 812.42.

5. Device Studies Exempt from IDE Requirements

Certain investigations may be exempt from the requirement for an IDE, if specified criteria are met. FDA exemption criteria are described in 21 CFR 812.2(c). Investigations that are exempt from IDE regulations still require IRB review and approval. Separate rules for studies of in vitro diagnostic devices are described at 21 CFR 809 subpart H.

Additional guidance regarding IDE requirements and exemptions is available at: Device Advice: Investigational Device Exemption (IDE).

C. Off-Label Use of an FDA-Approved Drug, Biologic or Device

"Off-Label use" means the use of legally marketed and/or FDA-approved drugs, biologics and devices for a purpose or in a manner not already approved by the FDA. Off-label use of a marketed product by a physician, when the intent is the "practice of medicine" (ie diagnosis, cure, mitigation, treatment, or prevention of disease in humans), does **not** require the submission of an IND or IDE or review by an IRB. If the off-label use of an FDA-approved product is used to collect data about the product's safety or efficacy, or for other non-diagnostic or non-therapeutic purposes, an IND or IDE is generally required if human research participants are involved. It is useful to consult with the IRB and with MIAP to determine when data collection for off-label use may be considered research.

FDA guidance for treating clinicians on off-label use is available at: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices - Guidance for Institutional Review Boards and Clinical Investigators.

III.EXPANDED ACCESS TO INVESTIGATIONAL DRUGS, BIOLOGICS AND DEVICES

The FDA has developed special mechanisms to expand access to promising investigational drugs, biologics, and devices ("investigational articles") for clinical treatment of patients without compromising the protection of human subjects or the thoroughness and scientific integrity of product development and marketing approval. Collectively, these mechanisms are known as "expanded access".

Regulatory support for expanded access to investigational products is provided through MICHR.

A. Expanded Access as Research versus Clinical Treatment

Although an investigational article used under the FDA expanded access mechanism is intended for the purpose of clinical treatment, the FDA may consider the treatment to constitute a "clinical investigation" (ie research), and require that data from the treatment be reportable in a marketing application. Conversely, under the HHS human research protection rules, patients who receive investigational articles through the expanded access mechanism are **not** considered research subjects, and outcomes of expanded access treatments may not be included in reports of research funded by federal agencies that follow HHS rules.

If the FDA considers the treatment under the expanded access mechanism to constitute "clinical treatment," an FDA accepted/approved IND or IDE submission or an amendment to an already existing IND or IDE is required prior to initiation of the clinical treatment.

Once submitted, an expanded access IND or IDE goes into effect 30 days after the FDA receives the IND or IDE submission, unless the FDA notifies the sponsor otherwise during that 30-day period. In many cases, the IND or IDE

will go into effect earlier, as soon as the FDA notifies the sponsor that treatment use may begin.

B. IRB's Role

In addition to an FDA-approved IND or IDE, expanded access requests must be approved by an IRB prior to administration of the treatment, and an IRB-approved informed consent form must be used to provide pertinent information to the patient and document his or her consent. The ONLY exception to this requirement is for individual patient **emergency use**, described more fully in Section IV, below.

C. Clinician Responsibilities

Any clinician providing treatment under an expanded access IND or IDE has particular additional responsibilities and obligations to the IRB and the FDA, if functioning as the FDA sponsor, and may have additional responsibilities to the company providing the investigational article. These include:

- Submission of adverse event reports to the IRB and to the FDA, if functioning as the study sponsor. Adverse events are submitted to the FDA sponsor if someone other than the treating clinician is the sponsor and by contractual agreement with a company providing the investigational test article;
- Annual reports to the FDA, if serving as the FDA sponsor; and
- Withdrawal of the IND or IDE with the FDA at the conclusion of the treatment period, if serving as the FDA sponsor.

IND annual reports and termination reports must be submitted to the IRB as well as the submission of IRB applications for continuing review and termination of the IRB application after the submission of the termination report to the FDA.

D. Expanded Access to Investigational Drugs and Biologics for Treatment Use

Investigational drugs and biologics are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug or biologic (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, patients are generally willing to accept greater risks from drugs and biologics that may treat life threatening and debilitating illnesses.

The expanded access IND regulations are categorized into three levels depending on the expected numbers of subjects to be treated and include:

- Expanded access for individual patients in emergency and non-emergency situations (21 CFR 312.310);
- Expanded access for intermediate-size patient population (21 CFR 312.315); and
- Expanded access for large patient population under a treatment IND (21 CFR 312.320).

The regulations also describe criteria that must be met to authorize expanded access, list requirements for expanded access submissions, and describe safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the drug. FDA guidance on expanded access INDs is available here:

- Expanded Access to Investigational Drugs for Treatment Use - Questions & Answers – Guidance for Industry
- Treatment Use of Investigational Drugs - Guidance for Institutional Review Boards and Clinical Investigators
- Individual Patient Expanded Access Applications: Form FDA 3926 - Guidance for Industry
- IND Applications for Clinical Treatment (Expanded Access): Overview)

Other mechanisms used by the FDA for expanded access to investigational drugs and biologics are described on the FDA website.

E. Right to Try

The Right to Try Act, or the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act, was signed into law May 30, 2018. This law is another way for patients who have been diagnosed with life-threatening diseases or conditions who have tried all approved treatment options and who are unable to participate in a clinical trial to access certain unapproved treatments. These treatments are limited to drugs and biologics that have advanced past Phase 1 clinical testing, have an active IND, and are not on clinical hold.

It is the position of Michigan Medicine that FDA's Expanded Access process provides critical patient protections in the use of investigational drugs, biologics and devices, and, therefore, Michigan Medicine leadership ***discourages*** *physicians and advanced practice providers (APPs) to access these investigational interventions for their patients through the Right to Try mechanism. Michigan Medicine requires all Right to Try requests be approved by IRBMED.*

Additional information on Right to Try is available here:

- Michigan Medicine Right to Try Guideline
- Right to Try - Food and Drug Administration

F. Expanded Access to Investigational Devices

There may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. Patients/physicians faced with these circumstances may have access to investigational devices under one of three main mechanisms by which the FDA may make an unapproved device available:

- Compassionate Use (or Single Patient/Small Group Access);
- Treatment Use;
- Emergency Use.

These mechanisms can be used during a certain timeframe in the IDE process if the criteria are met. FDA approval is required except in the case of emergency use. The mechanisms are summarized below.

1. Compassionate Use (devices)

The FDA "compassionate use" provision is intended to provide non-emergency access to an investigational device by an individual or small numbers of patients who the treating clinician believes will benefit from use of the device.

Additional requirements for compassionate use of devices are available from the FDA in: Expanded Access for Medical Devices - Compassionate Use (or Individual Patient/Small Group Access).

2. Treatment Use (devices)

A Treatment IDE provides a mechanism for a device that is not yet FDA approved to be used to treat a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. The treatment use provision of the IDE facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible. In the case of a serious disease, a device may be made available for treatment use after all clinical

trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use prior to the completion of all clinical trials. See Expanded Access for Medical Devices - Treatment Use from the FDA.

3. Emergency Use (devices)
See Section IV, below.

Additional information about the requirements for emergency use is available here.

Support for compassionate use of investigational devices is available through MICHR by contacting UM-Expanded-Access-Request@med.umich.edu.

IV.EMERGENCY USE OF INVESTIGATIONAL ARTICLES

Emergency use is defined as the use of an investigational drug, biologic, or device (ie investigational article) with a human subject in life-threatening conditions in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). The emergency use provisions in the FDA regulations, 21 CFR 56.104(c), provide an exemption from prior review and approval by the IRB as long as the emergency use is reported to the IRB within five working days. Any additional IRB-specific requirements are described in the relevant IRB SOPs.

Life-threatening, for the purposes of section 56.102(d), includes both life-threatening and severely debilitating, as defined below:

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

A. IRB Review

Prospective IRB review is required unless the conditions for the emergency use exemption from prior review and approval by the IRB are met (21 CFR 56.104(c) and 56.102(d)).

Generally, the FDA regulations do not provide for expedited IRB approval of emergency situations; full board approval of the report of the emergency use to the IRB is required. See FDA Guidance Emergency Use of an Investigational Drug or Biologic - Guidance for Institutional Review Boards and Clinical Investigators. The FDA may authorize a waiver of the requirement for review and approval at a convened IRB meeting for individual patient expanded access treatment use of investigational drugs if the physician obtains concurrence from the IRB chairperson (or designated IRB members) before the treatment use begins. See FDA Guidance Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers.

B. Single Use

The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that

it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

C. Informed Consent

Even for an emergency use, a treating clinician is required to obtain informed consent from the subject or the subject's legally authorized representative unless both the treating clinician and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- The subject is confronted by a life-threatening situation necessitating the use of the investigational article;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's legal representative; and
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the treating clinician's opinion, immediate use of the investigational article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the treating clinician should make the determination and, within five working days after the use of the investigational article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The treating clinician must notify the IRB within five working days after the use of the investigational device (21 CFR 50.23(c)).

D. Additional Guidance

Treating clinicians who seek to use an investigational article under the FDA emergency use provision are advised to consult IRBMED Guidance on this topic. Treating clinicians may also obtain advice from MICHR MIAP (Access-Request@med.umich.edu), the U-M Research Pharmacy and/or the Office of General Counsel.

E. Emergency Use of Investigational Drugs and Biologics

Emergency use of an investigational drug or biologic generally requires an IND. If the intended patient does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use.

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In an emergency situation, the request to use the drug or biologic may be made via telephone or other rapid means of communication. Before shipment or clinical treatment can begin, an FDA issued emergency IND is required. The IND that authorizes treatment to begin may be provided by an FDA official over the telephone. Such authorization requires the licensed physician or sponsor to file an IND application within 15 days of the date the FDA authorized the emergency use. In these situations, shipment of and treatment with the drug may begin prior to FDA's receipt of the written IND submission that is to follow the initial request (21 CFR 312.310).

Support for emergency use of investigational drugs and biologics is available through MICHR by contacting UM-Expanded-Access-Request@med.umich.edu.

1. Clinician Responsibilities

In the event that a treating clinician seeks to use an investigational drug or biologic to treat a life-threatening or severely debilitating condition under emergent circumstances, the following steps are generally required:

- Contact the manufacturer of the investigational drug or biologic to determine if they will make the drug or biologic available for emergency use and whether or not they will hold the IND.

- If an IND for the use already exists, notify the FDA-recognized sponsor (ie IND holder) of the emergency use.
- If an IND does not exist, or is not available for the emergency use under the existing IND, time permitting, obtain an independent assessment by a physician who is not otherwise participating in the clinical investigation.
- Obtain informed consent from the patient or legally authorized representative, if possible. See IRBMED FDA expanded access informed consent template.
- Notify the IRB of use as soon as possible (prior to initiating treatment, if possible, or within five working days of the use at the latest).

After the emergency, the treating clinician must:

- Report the emergency use to the IRB (by eResearch Single-patient Expanded Access Drug or Biologic application) within five working days and otherwise comply with IRB requirements.
- Obtain an independent assessment by a physician, who is not otherwise participating in the clinical investigation, within five working days of the use, if consent could not be obtained from the patient or legally authorized representative prior to the use.
- Evaluate the likelihood of a similar need occurring again and, if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IND for subsequent use. *NOTE: FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.*
- If holding the IND, provide the FDA, within 15 working days of emergency use, a written summary of the conditions constituting the emergency, subject protection measures and results; otherwise, provide the summary to the IND holder.
- If an IND has been submitted and disapproved by the FDA, the investigational article may not be used even in an emergency.
- If the treating clinician is the FDA sponsor and holds the IND, at the conclusion of the treatment, submit a final report (summary report) to the FDA and withdraw the IND.

2. **FDA Guidance on Emergency Use of an Investigational Drug or Biologic**
   - Emergency Use of an Investigational Drug or Biologic - Guidance for Institutional Review Boards and Clinical Investigators
   - Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers, Guidance for Industry.
   - Treatment Use of Investigational DrugsGuidance for Institutional Review Boards and Clinical Investigators.

F. Emergency Use of Investigational Device

In general, an unapproved medical device may only be used on research participants when the device is under clinical investigation and when used by investigators participating in a clinical trial. However, the FDA recognizes that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, or to prevent an irreversible morbidity when no other alternative therapy exists.

Emergency use of an unapproved device may occur when: (i) an IDE for the device does not exist, (ii) when a treating clinician wants to use the device in a way not approved under the IDE, or (iii) when a treating clinician is not an

investigator under the IDE. In each situation, emergency use of an unapproved device may occur without prior approval from the FDA or an IRB.

Support for emergency use of investigational devices is available through MICHR by contacting UM-Expanded-Access-Request@med.umich.edu.

1. Clinician Responsibilities

If a treating clinician intends to treat a patient with an unapproved medical device in an emergency situation, the FDA expects the treating clinician to:

a. Determine that:
- The patient has a life-threatening condition that needs immediate treatment (including serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity);
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

b. Assess the potential for benefit from the use of the unapproved device;

c. Have substantial reason to believe that benefits will exist.

In the event that a device is used in circumstances meeting the criteria listed above, the treating clinician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

- Informed consent from the patient or a legally authorized representative;
- Clearance from the institution as specified by their policies;
- Concurrence of the IRB chairperson;
- An independent assessment from an uninvolved physician prior to, or after, use, as appropriate to the situation, if informed consent cannot be obtained; and
- Authorization from the IDE sponsor, if an approved IDE exists for the device.

After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur:

- As soon as possible and no later than five working days of the use, report the emergency use to the IRB in an eResearch Single-patient Expanded Access Device Use application.
- Obtain an independent assessment by an uninvolved physician within five days of the use, if consent could not be obtained from the patient or legally authorized representative prior to the use.
- Evaluate the likelihood of a similar need occurring again and, if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for subsequent use. *NOTE: FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.*
- If an IDE exists for the device, within five working days of the use, the treating clinician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. The sponsor must report the use to the FDA via a supplement within five working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed (as discussed above), and patient outcome information.

- If no IDE exists, within five working days of the use, the physician should submit a follow-up report on the use of the device to the FDA, including a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

2. FDA Guidance on Emergency Use of Investigational Devices

- Expanded Access for Medical Devices – Emergency Use
- IDE Application: IDE Modifications

V. PLANNED EMERGENCY RESEARCH USING INVESTIGATIONAL ARTICLES

Planned emergency research is a rarely used, but important, type of research that allows participants to be enrolled without prior informed consent. It differs from emergency use of a test article described above and has additional, specific requirements for investigators and the IRB (21CFR 50.24).

Researchers who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB.

For more information about planned emergency research using an investigational article see FDA guidance on Exception from Informed Consent for Emergency Research.

VI.HUMANITARIAN USE DEVICES (HUD) AND HUMANITARIAN DEVICE EXEMPTIONS (HDE)

A FDA-designated Humanitarian Use Device (HUD) is intended to benefit small populations (<8,000 individuals in the United States per year) with a rare condition for which effectiveness cannot be readily determined prior to marketing. Before the treating clinician may use a HUD, the FDA-recognized sponsor must obtain a Humanitarian Device Exemption (HDE). The treating clinician must also obtain IRB approval (via full board approval), unless the use of the HUD meets criteria for emergency use. Informed consent documents must not refer to the humanitarian use of the device as "research", unless the HUD is being used in a clinical investigation.

Additional information about HUDs and HDEs:

- Humanitarian Device Exemption (HDE) Regulation: Questions and Answers - Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff
- Humanitarian Device Exemption (HDE) Program - Guidance for Industry and Food and Drug Administration Staff

VII.FDA SPONSORS AND SPONSOR-INVESTIGATORS

As included in the table in section I, FDA regulations at 21 CFR 312 and 21 CFR 812, define "sponsor" and "sponsor-investigator," as follows:

- A "sponsor" is an organization or individual that initiates and takes responsibility for a clinical trial or other FDA-regulated project involving a drug, biologic or device.
- A "sponsor-investigator" is an individual who both initiates and conducts an investigation of an FDA-regulated drug, biologic or device and under whose immediate direction the drug, biologic or device is administered or dispensed. The term does not include any person other than an individual.

Part of an FDA sponsor's or sponsor-investigator's responsibility is to obtain any required IND or IDE from the FDA. For that reason, a "sponsor" is sometimes referred to as the IND or IDE "holder".

A. University/University Employee as Sponsor/Holder

The University, itself, generally does not "sponsor" (or "hold") INDs or IDEs and a University faculty or staff member ("employee") may not apply for an IND or IDE **on behalf** of the University without written approval of the Vice President for Research or his/her designee.

University employees may, however, act as "sponsors" or "sponsor-investigators" and hold their own INDs or IDEs if they: (1) have adequate training, experience, and support to properly conduct and monitor the relevant project activities, and (2) are able and willing to comply with relevant regulatory and institutional requirements.

B. Sponsor-Investigator Responsibilities

Investigators who initiate and submit IND or IDE applications to the FDA assume the responsibilities of both the investigator and the sponsor. The responsibilities of a sponsor are described at 21 CFR 312.50-312.59 and 812.40-812.47. Under FDA regulations, an academic sponsor or sponsor-investigator has the same obligations as a multi-national pharmaceutical manufacturer that sponsors or holds an IND or IDE.

When a U-M employee applies to be the sponsor or sponsor-investigator of an IND or IDE, they make a personal commitment to the FDA to comply with a complex set of requirements (21 CFR 312, 812, and others) regarding the investigational article itself and the overall management of the project(s), as described below in Section VIII. In addition, any U-M employee serving or seeking to serve as the sponsor or sponsor-investigator of an IND or IDE in conjunction with his or her University appointment must also:

- Utilize MICHR MIAP services for document preparation assistance, application review, and maintenance of an active IND or IDE;
- Complete an eResearch application and obtain IRB approval prior to initiating research;
- Complete a MICHR MIAP training session on FDA Sponsor-Investigator requirements;
- Ensure proper monitoring of the study and upload the monitoring reports in the eResearch IRB application;
- Archive all documents, related to the IND or IDE, including all FDA submissions and correspondence, in the eResearch IRB application.

C. Clinical Trials Registration

The holder of the IND or IDE (the IND or IDE "sponsor" or "sponsor-investigator") for a clinical investigation is responsible for registering the trial on ClinicalTrials.gov within 21 days after the enrollment of the first subject. When seeking informed consent from subjects, investigators must ensure that the informed consent document and process include a statement that the trial is registered with ClinicalTrials.gov, in accordance with the provisions of 21 CFR 50.25(c). This statement is part of the U-M IRBMED Informed Consent template.

For additional information, see the HRPP guidance on Clinical Trials Registration & Results Reporting.

D. Noncompliance

Serious or continuing noncompliance with the obligations of a sponsor or sponsor-investigator may lead to University or FDA restrictions on the ability of the faculty member to enter into future agreements with the FDA. See Part 12 of this OM.

FDA guidance for sponsor-investigators is available at:

- Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)
- IDE Responsibilities

E. Manufacturer of Investigational Articles

In the rare event that a U-M employee intends to manufacture an investigational article, advice must be sought from one or more the following U-M offices at the earliest opportunity and prior to use of the article with humans (even for feasibility assessment): IRB, Office of the General Counsel, U-M Office of Research, UMMS Office of Regulatory Affairs. These offices will alert other offices as applicable.

VIII.INVESTIGATOR AND IRB RESPONSIBILITIES FOR FDA-REGULATED RESEARCH

A. Ensuring Review by Appropriate IRB

The investigator conducting FDA-regulated research must ensure that an appropriate University IRB (or other IRB with which U-M has established a reliance agreement) is responsible for the initial and continuing review, and approval of modifications to the research, in accordance with the FDA requirements at 21 CFR 50 and 56. The U-M IRBs are registered with both the FDA and the OHRP. Changes may be made to a research protocol only after notifying the sponsor and receiving approval from the IRB, except when necessary to eliminate apparent immediate hazards to subjects. Informed consent must be obtained from all prospective subjects prior to enrollment in the research, unless the IRB approved a waiver of informed consent.

B. Verification of IND or IDE Acquisition Prior to Release of Final IRB Approval

Through the eResearch IRB application, investigators answer a series of questions designed to determine whether or not an IND or IDE may be required for a research project. If it appears that an IND or IDE may be required, the reviewing IRB will require one of the following in order to verify IND or IDE acquisition prior to release of final IRB approval:

- Written FDA documentation that an IND or IDE has been granted (including the IND or IDE number), or that an existing IND or IDE has been amended, as appropriate, to cover the specific project in question; or
- Written documentation that the FDA's time for consideration of an IND application for the research project in question has lapsed without a notice of disapproval or conditional approval and without a request for additional information (the investigator must still provide the IRB with FDA documentation of the IND number assigned by the FDA when the FDA acknowledged receipt of the IND application); or
- Written documentation that the FDA has approved the IDE application; or
- Written documentation of the FDA's determination that an IND or IDE is not required.

As described in section II.B, for research involving an investigational device, once the investigator demonstrates to the IRB's satisfaction that the research meets the FDA's criteria for a NSR device study, IRB approval of the research and documentation of its NSR decision is sufficient.

C. Oversight of FDA-Regulated Research

In addition to ensuring IRB review and approval, and in addition to general researcher responsibilities outlined in Part 6 of this OM, a clinical investigator conducting FDA-regulated research must personally conduct or supervise the study as specified in the signed investigator statement, the investigational plan (protocol), any applicable sponsor agreement, and the IRB-approved application and associated materials.

Before initiating a research project, the clinical investigator must read and understand the information in the investigator's brochure or similar documentation, including the risks and potential benefits of the investigational article.

The investigator is responsible for ensuring that all sub-investigators and other research team members assisting in the conduct of the study are informed about their obligations and are adequately trained to carry out their responsibilities competently and appropriately. Investigator responsibilities are described in further detail at 21 CFR 312.60-312.69 (drugs and biologics); and 21 CFR 812.100-812.110 (devices).

See, also, FDA guidance on Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects.

D. Investigational Article Accountability

During the research project, the researcher is responsible for all aspects of protocol implementation, including proper receipt, storage, security, use, and disposal of the investigational article, and all related necessary documentation for the investigational product. In the eResearch application for IRB approval, the researcher must describe his or her plan to assure that investigational articles are used only in approved protocols and under the direction of approved researchers. Deviations from these plans are permitted only in emergency circumstances, consistent with FDA requirements and University policies on emergency use, or to avoid immediate harm to subjects. An IRB may not approve a proposed research project that does not include satisfactory plans for investigational article accountability. Test article accountability procedures are described in more detail in Part 3, Section III.C.6.i of this OM.

E. Charging for Investigational Articles

When the FDA-recognized sponsor or sponsor-investigator intends to charge subjects for investigational articles or related treatment or services, he or she must comply with all IRB policies (eg to ensure that the charges are appropriate and equitable, and to require disclosure of the charges in the informed consent document and process), institutional billing policies, and professional ethics, as well as the FDA guidelines at: Charging for Investigational Products - Guidance for Institutional Review Boards and Clinical Investigators. The charge may not exceed an amount that is necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational article.

FDA guidance on charging for investigational drugs and biologics is available here: Charging for Investigational Drugs Under an IND – Questions & Answers – Guidance for Industry.

F. Records and Documentation

The researcher must ensure the creation and maintenance of complete and accurate research records, such as informed consent documentation, case report forms, correspondence files, and other relevant information for record keeping purposes and possible inspection by institutional officials, outside sponsors, and regulatory agencies.

In addition, the names and commitment of study team members, as well as their responsibilities, qualifications, and study-specific training must be clearly documented, including, as appropriate, on FDA Form 1572 (drugs and biologics), investigator agreements (devices), and delegation logs.

1. Electronic Records

FDA regulations at 21 CFR Part 11 set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. Part 11 is intended to

ensure that information submitted to and considered by the FDA is readily accessible and auditable in order to validate its accuracy.

The University has conducted and documented a self-assessment of eResearch compliance with 21 CFR Part 11 (Self Assessment of eResearch Compliance) and has issued an electronic signature certification statement (Certification of Electronic Signatures). Similar documentation of Part 11 compliance of Michigan Medicine medical record systems is available in IRBMED guidance at: Electronic Records and Electronic Signatures (21 CFR Part 11).

For additional guidance regarding Part 11 compliance, see FDA Guidance: Part 11, Electronic Records; Electronic Signatures - Scope and Application.

2. Record Retention

The FDA requires that records be retained in compliance with applicable laws, regulations, policies, and agreements. The required manner and duration of record retention, as specified in these rules, may vary widely and depend on the characteristics of the particular research project or other related activity. Clinical investigators are also advised to consult with the relevant FDA-recognized sponsor before disposing of records associated with a particular research project or related activity. U-M institutional guidance on record retention is available at U-M Medical School Record Keeping Guidelines.

G. Required Reporting

The researcher must comply with FDA reporting requirements including timely submission of annual reports. The researcher must also ensure that adverse events and other unanticipated problems involving risks to subjects or others are reported to the FDA sponsor and the IRB in a timely manner and be consistent with the IRB approved reporting plan in the study protocol. In addition, promptly after receipt, researchers must provide to the IRB copies of any audit or inspection reports, warning letters, debarment notices, or similar documents issued by sponsors, government regulators (such as the FDA or NIH), internal oversight units, or other organizations with oversight responsibilities.

More information on adverse event and other reporting requirements is available in IRB Standard Operating Procedures and in IRBMED Guidance.

H. ICH-E6 and GCP

The ICH Efficacy Guideline (E6) on GCP is an international standard established to promote the ethical and scientifically sound design, conduct, recording, and reporting of human clinical trials. When a research protocol or agreement specifies that ICH GCP will be followed, the FDA and U-M oversight authorities will enforce compliance with GCP requirements. In addition, the NIH has established the expectation that researchers involved in the conduct, oversight, or management of NIH-funded clinical trials be trained in GCP (Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials) link is external).

Additional information about GCP guidelines is available at: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) and in Frequently Asked Questions: NIH Policy on Good Clinical Practice (GCP). Instructions for how to complete GCP training are available on the HRPP website.

I. FDA Inspections of FDA-Regulated Research and Related Activities

The FDA conducts routine and for-cause inspections of clinical trials, investigators, and IRBs, in order to validate data that is under FDA consideration, verify protection of research participants, confirm general compliance with FDA and other applicable regulations, policies, and agreements (including sponsor agreements), and investigate complaints and

self-reports of non-compliance. FDA inspections are typically scheduled in advance, but may be conducted without advance notice.

When contacted by the FDA to schedule an inspection (or when the FDA has arrived without advance notice), the investigator or a member of the research team is expected to contact one of the following offices at the earliest opportunity: IRB, Office of the General Counsel, U-M Office of Research, UMMS Office of Regulatory Affairs.

PART 9: Conflicts of Interest and Commitment

Describes how conflicts of interest and commitment in research can adversely impact the integrity of research results and the confidence of prospective volunteers in the research enterprise. The University seeks to identify, disclose, and eliminate or manage conflicts to avoid these negative repercussions.

I. APPLICABLE POLICIES

The University follows a number of institutional, state, and federal bylaws, policies, procedures, and practices concerning employees' outside financial or management interests that could form the basis of a conflict. These include, but are not be limited to:

- U-M Standard Practice Guide (SPG) - 201.65-1 (applies to all U-M employees)
- Policy for the Identification and Management of Conflicts of Interest in Research, Sponsored Projects, and Technology Transfer
- List of outside interest disclosure criteria
- U-M Policy for Institutional Conflicts of Interest in Research
- State of Michigan: Contracts of Public Servants with Public Entities (Act 371 of 1968)
- State of Michigan: Conflict of Interest (Act 318 of 1968)
- NIH (PHS) COI Policy
- NSF COI Policy

School, college, and unit policies on COI and commitment augment these policies and may address the conditions that allow an individual with a significant financial interest to be a researcher. The Medical School's COI policy is of particular importance to the HRPP, as the researchers in the U-M Health System conduct the majority of human subjects research with *greater than minimal risk* that also presents a financial or management conflict of interest (and also conduct the majority of human subjects research that needs disclosure and COI management regardless of risk level).

Generally, policies regulating outside interests seek to promote the following values:

- Objectivity and integrity in research;
- Open publication of research results;
- Appropriate use of sponsor or University funds;
- Maintenance of appropriate relationships with and fulfillment of obligations to colleagues, students, and other trainees;
- Fulfillment of administrative duties;
- Integrity of academic decision-making;
- Avoidance of "pipelining" University intellectual property to an outside entity outside of an appropriate research agreement; and
- Protection of and appropriate informed consent with research participants.

The HRPP requires outside interest disclosure for study personnel when submitting or amending an IRB application for human subjects research. Study personnel listed on the IRB application are required to answer COI questions when they accept their role on the project.

II. CONFLICTS OF INTEREST OF INVESTIGATORS AND RESEARCH STAFF

There are three main steps to the COI review process for human subjects research:

1. Identification and disclosure of outside interests by researchers and research staff.

2. Review of outside interest disclosures by a U-M COI review committee to determine if a conflict of interest exists.
3. Risk/benefit analysis by an IRB.

A. Identification and Disclosure of Outside Interests Related to Human Research

Outside interests or potential conflicts of interest on the part of researchers and research staff (and their spouses, domestic partners, or dependents) relevant to the integrity of human subjects research include, but are not limited to, the following:

- Ownership (eg equity, shares or stock options) in an outside company or other entity that has activity related to the research;
- Compensation, other payments or items of value from an outside entity (eg consulting fees)
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement; and
- Paid or unpaid activities and relationships (eg serving in a leadership position for the agency or company sponsoring the research, volunteer activities, consulting or serving on a scientific advisory board).

The University provides training for the disclosure of outside activities, relationships, and interests through the M-Inform disclosure system and through unit policies.

Information about relevant outside interests are identified from a number of transactions that include:

1. Sponsored Project Proposals

Every proposal for externally sponsored research requires submission of a completed eResearch PAF. This electronic form summarizes information about the proposal and is used for U-M administrative review and approval. The PAF requires the PI to attest to whether or not any proposed researcher on the sponsored project (and/or their spouse, domestic partner or dependents) has a significant financial interest related to the proposed research. If a significant financial or management interest is indicated, formal disclosures are required in M-Inform, the University's outside interest disclosure system.

2. IRB Application

As part of the eResearch IRB application, researchers and study team members indicate if they (and/or their spouses, domestic partners, or dependents) have an outside interest with a non-UM entity associated with the research in one of the following ways:

- The entity sponsors the research;
- The entity's products are used in the research;
- The entity licensed an invention (eg device, compound, drug, software, evaluation instrument, etc.) developed by a study researcher or team member, which is being used in the research;
- Part of the research project will be subcontracted to the entity;
- Other type of relationship not listed above.

If an outside interest is related in a manner as identified above, formal disclosure from the individual is required in M-Inform and in the IRB application.

Should a related interest develop during the course of a research project, the researcher must both update M-Inform and ensure the related interest question in the IRB application is updated within 30 days of the new interest (contact the PI or the COI Office for assistance). If a study has been approved, an amendment will be needed to update the IRB application.

3. Disclosures first received by schools and colleges pursuant to COI/COC policies

U-M schools and colleges have disclosure processes for reporting outside activities that are outlined in their respective unit Conflict of Interest/Conflict of Commitment (COI/COC) policies. These disclosures are

reviewed for identification of potential COIs not captured by other mechanisms. Potential COIs related to research or technology transfer are referred to the applicable COI review committee.

4. Sponsored project and technology transfer negotiations

To assist in complying with State of Michigan statutes, sponsored project and technology transfer negotiators identify and forward to the COI review committees proposed research or licensing agreements in which a University employee has a significant financial interest in or management role with the sponsor of the research or is the recipient of the license. The applicable COI committee (COI-UMOR or MEDCOI) reviews these transactions and the associated outside interest disclosures to determine if COI exists and requires management. The COI committee alerts the appropriate IRB when they receive disclosures, or are notified of situations, associated with human subjects research.

B. Conflict of Interest Review and Management

When an IRB application includes an indication of a related outside interest, a U-M COI committee conducts a risk review to:

- Ensure appropriate management of the conflict in order to eliminate or reduce risk to the project, the researchers, and the University.
- Provide guidance on applicable informed consent language in order to notify and protect the study participants.

The COI Committee reviews the M-Inform disclosure, the IRB application, and applicable related transactions (eg research proposals and license and option agreements) to determine the extent to which:

- Key researchers and study team members have significant financial or management interests in research;
- Research participants are involved in the proposed research;
- Individuals in the administrative hierarchies of the key researchers have financial interests in the research;
- The University itself has a financial interest in the research.

Representatives of the IRBs, the ORSP, and Innovation Partnerships attend COI committee meetings as consultants, as appropriate. They provide source information regarding human subjects research, sponsored projects, contracts and agreements, and University equity holdings in proposed sponsors of research or proposed licensees.

Individuals with significant financial or management interests in a research project may be allowed to participate in that project only with special justification and a COI committee determination of compelling circumstances. Conflict of interest management plans include specific management provisions to protect research participants.

ORCR conducts routine reviews for compliance with COI management plans.

C. IRB Risk/Benefit Analysis

The IRB has access to COI and ICOI management plans established for study team members listed on the IRB application and for institutional interests related to the application. IRBs include COI/ICOI risk in their risk/benefit analysis and may place additional restrictions on the conflicted individuals or the research in its entirety, up to and including disapproving participation of a conflicted individual or disapproving the research. IRBs have final authority to determine whether any disclosed interest and its management allows the research to receive IRB approval. IRBs typically require disclosure to potential research participants in the informed consent document if a key researcher, study team members, or the institution itself has a financial interest in the research. Should the IRB determine conflict management imposed by any of the U-M COI Committees should be altered (e.g., requiring additional measures or removing a requirement), the IRB will contact the appropriate COI Office to request revision of the conflict management plan.

III. CONFLICTS OF INTEREST OF IRB MEMBERS, CONSULTANTS AND STAFF

Each IRB has a SOP for identifying and avoiding COI in reviewing and approving research and in managing office functions. The SOP describes the process for re-assigning reviews to a non-conflicted member when an IRB member is assigned to a review in which he or she has a COI in the research.

An IRB member or a consultant with the IRB will not be assigned to review an application if he/she (and/or their spouse, domestic partner, or dependents):

- Is a researcher or a team member of the study;
- Has a significant financial interest in the research, such as the criteria listed above;
- Has other conflicts that the member/consultant, the IRB, the COI Committee or the UMOR believes might hamper that individual's ability to perform an impartial review.

IRB members and consultants are also prohibited from participating in the following activities in which they have a conflict of interest:

- Board review of the applicable IRB application, including meeting attendance, quorum count, deliberations for, and the vote on the disposition of the application;
- Review by expedited procedure;
- Review of unanticipated problems involving risks to research participants or others;
- Review of non-compliance with the regulations or the requirements of the IRB.

The member or consultant may, however, be invited by the IRB meeting to provide information relevant to the IRB's consideration of the application.

IV. INSTITUTIONAL CONFLICTS OF INTEREST

In support of the public interest, the University, acting as an organization, may form relationships with, enter into affiliations or agreements with, or invest in outside companies or organizations for mutual benefit. Through these relationships, the University can translate the knowledge of its faculty, staff, students and trainees into socially useful applications, enrich education and research with practical experience, purchase goods and services, and secure financial returns to support the University's missions. These relationships may place the University in situations of "Institutional Conflict of Interest" (ICOI) when accepting grants from, making investments in, or engaging in activities with these outside companies or organizations that compromise or appear to compromise the University's fulfillment of its mission in an objective unbiased manner ("Direct Institutional Conflict of Interest" or "Direct ICOI").

An ICOI can arise when any interest of the University or the personal financial interests of key University leaders has the possibility of compromising the judgment or behavior of faculty or staff or leaders themselves with respect to teaching and student affairs, appointments or promotions, uses of University resources, interactions with research participants or patients, objectivity of research, or other activity of the University. These interests include, but are not limited to:

- Licensing or technology transfer agreements;
- Income from University investments;
- Potential increase in the value of equity held by the University in a faculty start-up;
- The prospect or receipt of gifts to the University;
- Personal investments, intellectual property rights, or income from consulting or other activity of key University leaders;
- Other financial interests of the University.

Outside relationships or financial interests of the University's leadership with outside companies or organizations may raise issues related to ICOI by virtue of the leaders' ability to influence decisions about the University's relationships, or processes, policies or functions of the University. These outside relationships or financial interests may appear to interfere or actually interfere with the obligation for University leadership to act in the University's best interests. The Standard Practice Guide 201.65-1 applies to all employees of the University. Key University leaders are required to report to their superiors (department chairs to deans, deans to the provost, executive officers to the President, and the President to the Regents) any outside activity and financial or other interest that could affect the performance of any of their leadership obligations. Interests are eliminated or managed as deemed appropriate by the office receiving the disclosure.

The following *Institutional Conflict of Interest Principles* have been endorsed to guide the development and refinement of strategies to assure the highest level of integrity to maintain the public trust. In all relationships and activities, the University and its leadership are expected to abide by the highest standards of conduct in education, research and public service. The Principles are intended to operate in conjunction with other University policies related to conflict of interest and commitment, including unit-based policies on conflict of interest and commitment mandated by Standard Practice Guide 201.65-1.

- The University and its leadership are responsible for furthering and collectively protecting the University's missions of education, research and public service;
- Commercial collaborations and the transfer of technology between the University and industry are encouraged and play a critical role in furthering the University's missions by generating new discoveries and facilitating the use of those discoveries for the public benefit;
- Direct and Indirect ICOIs that are not disclosed and remain unmanaged may appear to interfere or actually interfere with the obligations of the University and its leadership to further and protect the missions of the University;
- No outside relationship or financial interest of the University or its leadership should interfere with or compromise the missions of the University;
- The ICOI management process will ensure that the activities of the University and its leadership remain principled, capable of withstanding intense public scrutiny and protective of the University's missions;
- The ICOI management process will be rational, well publicized, transparent and consistently applied.

Failure to abide by ICOI policies may subject offenders to potential sanctions ranging from verbal warning to termination of employment. (See: Regent Bylaw 5.08 & 5.09 and Standard Practice Guide 201.12)

Conflicts of interest resulting from interests of the institution itself are addressed by various institutional policies and practices.

The University of Michigan is addressing institutional COI in research and in human subject research, specifically, in a stepwise fashion designing policies and implementing procedures first in high-risk circumstances.

When conducting reviews of research projects, the COI committees have access to information on any University equity in an outside organization associated with the research as well as information on any significant financial or management interest in start-up companies by University administrators. The COI committee may also inquire about gifts to the University. From time to time the two COI committees may seek consultative advice from each other or refer a situation in its entirety to the other committee to manage a potential COI situation associated with significant outside interests.

The University's equity in start-up companies is managed as part of the University's broader investment portfolio and therefore no different from other institutional investments. This helps avoid bias or favoritism. The Chief Financial Officer (CFO), not the VPR, coordinates University investments utilizing outside managers to assist with investment strategy. A determination to liquidate the University's investment in a holding is never a research decision. The University's Policy for Institutional Conflicts of Interest in Research outlines the principles and procedures for the identification, review, and management of potential institutional conflicts of interest to ensure that research activities are conducted without untoward influence resulting from certain payments for the transfer of technology, university

equity holdings outside the university's endowment, gifts to the university, or significant financial interests of senior management personnel. This policy establishes the ICOI Committee, which is appointed by the President to review potential conflicts and make recommendations to the President for institutional decision. The committee membership includes at least two individuals unaffiliated with the U-M.

PART 10: Sponsored Research

Describes policies and procedures for the administration of sponsored project agreements for human research.

I. ROLE OF THE OFFICE OF RESEARCH AND SPONSORED PROJECTS

The Office of Research and Sponsored Projects (ORSP) enables and safeguards the conduct of research and other sponsored activity for the U-M. ORSP applies specialized regulatory, statutory and institutional policies in order to balance the University's mission, the sponsor's objectives, and the researcher's intellectual pursuits. ORSP assists faculty and staff members in all aspects of externally funded research projects and other scholarly activities, such as finding funding, preparing and submitting proposals, negotiating sponsor agreements, setting up financial accounts, managing and administering projects and closing out projects.

II. AGREEMENTS WITH SPONSORS

ORSP submits sponsored research proposals to external agencies, negotiates the terms of agreements consistent with the mission and goals of the University and HRPP and all applicable laws and policies, and arranges for the establishment of appropriate financial accounts when a project is awarded. ORSP uses a campus-wide application for electronic Routing and Proposal Management (eRPM) to obtain and record information about the proposed activity. eRPM information system includes whether a research proposal involves human research as well as the status of the IRB determination. ORSP checks for IRB determination before setting up an account for a project and activating an award. When negotiating sponsor agreements, University policy requires agreements involving human research to include provisions addressing the following, when applicable:

- Assurance of compliance with human research protection requirements;
- Medical care for research-related injury;
- Communication of findings that could affect safety of participants, or their willingness to participate, or influence the conduct of the research;
- Dissemination of research findings.

A. Assurance of Compliance with Human Research Protection Requirements

University policy requires that all sponsored activity at the U-M comply with human research protection requirements mandated by federal regulatory agencies, State Laws, accreditation standards and university policy.

In each sponsor agreement, the University includes a provision referencing the University's responsibility to conduct the research in accordance with applicable law and applicable organizational and industry ethical standards relating to protecting human research participants. In sponsored clinical trial agreements, the University includes additional provisions that incorporate, by reference, the written study protocol and allow the sponsor and regulatory authorities, such as the FDA, the right to inspect the University's property and documents related to the performance of a trial to ensure it is being conducted in accordance with the protocol and applicable law.

B. Medical Care For Research-Related Injury

1. Provisions in Sponsor Agreements

Before any clinical research involving human research participants begins, arrangements for medical care for research-related injuries are defined, including who will provide such care and who will be responsible for paying for the care. Various University personnel including the PI, his/her administrator, the clinical

coordinator, the clinical research Calendar Review and Analysis Office (CRAO), the clinical trials planning unit, or the ORSP project representative, may conduct discussions with the sponsor concerning this issue. When contracting with sponsors, the University first attempts, when appropriate, to require the sponsor be responsible for the payment of medical care provided for a research-related injury, illness or adverse event.

2. Informed Consent Documents

For greater than minimal risk research, the Common Rule requires that researchers present information to research participants about medical and financial responsibility for research-related injuries in the informed consent document so that participants can consider this information before agreeing to participate. The informed consent document must specify financial and medical care responsibilities for research-related injuries and include instructions concerning where medical treatment should be sought if injury occurs and whom to contact in the event of a research-related injury.

The sponsor agreement generally sets forth information concerning research-related injuries consistent with the information provided to the research participant for research projects where this is applicable. CRAO compares the informed consent document and the contract provision to ensure that the language in each regarding research-related injuries is in agreement. For research not subject to CRAO review, the IRB considers the information regarding research-related injuries provided in the informed consent, seeking input from other institutional authorities, as indicated.

3. Billing Calendars

Faculty and staff conducting clinical trials containing billable items and services must submit a billing calendar as part of the IRB application process. All items and services to be utilized in the study as set forth in the protocol must be documented in the billing calendar at the designated time points with the appropriate designation.

CRAO reviews all human research protocols, informed consent documents, budgets, and contracts containing billable items and services irrespective of payer, and each research protocol undergoes a Medicare Coverage Analysis to ensure billing compliance.

C. Communication of Findings that May Affect the Safety of Human Research Participants or Their Willingness to Participate, or Influence the Conduct of the Research

The University requires sponsors to provide written plans for communicating routine and urgent safety information that could:

- Affect the safety of participants;
- Affect the willingness of participants to continue participation;
- Influence the conduct of the research; or
- Alter the IRB's approval to continue the study.

The sponsor must also agree to promptly report to the researcher any information that could directly affect the health or safety of past or current study participants or influence the conduct of the study, including but not limited to the study results and information in site monitoring reports and data and safety monitoring committee reports as required by the protocol. In each case, the researcher and the University shall be free to communicate these findings to each study participant and the IRB, per their reporting guidelines.

The above requirements may be addressed in a master agreement, a project-specific agreement or any of their respective incorporated attachments such as a study protocol.

D. Dissemination of Findings from the Research

1. Policy on Disseminating Research Findings

The principles of open scholarly exchange and academic freedom are integral to U-M's mission. These principles are referred to as "*Openness in Research*" and are set forth by the Regents' policy, under the Standard Practice Guide (SPG 303.01). It ensures (in part) that U-M:

- reserves the right to publish and disseminate information resulting from sponsored research;
- can maintain the confidentiality of the sponsor's confidential information, when necessary;
- does not conduct research that restricts the freedom to disclose the existence of the agreement.

SPG 303.01 defines three types of restrictions on dissemination of research findings: "Standard Restrictions", "Non-Standard Restrictions", and "Classified Research Restrictions". "Standard Restrictions" include provisions giving a sponsor the right to review, comment, and protect confidential information and intellectual property. Sponsor-imposed restrictions that fall within the above parameters are reviewed and approved through the regular PAF process and do not require additional approvals. "Non-Standard Restrictions" and "Classified Research Restrictions" require explicit review and approvals. Additional information is provided on ORSP's website.

2. Review/Comment and Delay Provisions

University policy permits a sponsor a reasonable period of time, usually not to exceed 180 days, to review a proposed publication or other dissemination of research results for:

- Comment (not for prior approval);
- Protection of sponsor's confidential information;
- Possible participation in protection of sponsor's intellectual property.

In instances where the researcher wishes to disclose the results in a format other than submission to a journal, (ie slides, posters, conference, etc.), negotiation with the sponsor typically provides for a reduced review period. Any publication delay of greater than 180 days must be reported to the Office of the Vice President for Research (OVPR), via an Agreement Acceptance Request (AAR).

During the review and comment period, a sponsor may recommend any changes to the publication it reasonably believes are necessary for scientific purposes.

3. Single Site Study Provisions

When the University is the only site participating in a sponsored research study (this more typically occurs with an investigator-initiated trial), the publication protection of the research agreement will include the review/comment period and the potential delay for confidential information and intellectual property as well as the right of the sponsor to require the removal of confidential and proprietary information provided by the sponsor prior to publication or dissemination of findings.

4. Multi-Center Study Provisions

In multi-center studies, where numerous sites participate in the study, the sponsor may require the pooling of the information from all the sites and an initial publication based on the aggregated data. University policy recognizes that multi-site publication may be the best way to assure the integrity of multi-center trial results. The policy allows for a reasonable and determinate time delay for publication by the University of its site results following the initial multi-site publication or after the sponsor indicates that such publication will not take place.

The usual period of delay for the University to publish in such instances is between 12-18 months from the completion of the study at all sites. This delay period is often triggered once data collection from all trial sites is complete and the overall study results database has been locked with the only remaining activity analysis of the aggregate data by the study sponsor. After this delay period has lapsed, the University researcher can present the results from his/her site to the sponsor for the review and comment period, and to determine if any confidential or proprietary information should be removed prior to publication or dissemination of findings. The sponsor is required to provide notice to the University when the study is completed to allow the University to compute the publication delay period.

5. Compliance with Federal Disclosure Requirements

Sponsor agreement provisions regarding dissemination of research findings must not prevent full compliance with federal disclosure provisions, such as those covered by the FDA Amendments Act requiring reporting of certain results in ClinicalTrials.gov. See Part 11 of this OM.

6. Dissemination to Research Participants

When participants request information concerning a completed study, they are provided with information as described in the IRB approved consent form. In addition, if adverse events are experienced at the University or have occurred at other sites involved in the trial and are made known to the University via broadcasting of such instances from the sponsor or other sites, the University may revise the informed consent to include notice of any safety issues and may also require re-consent of the research participants. In sponsor agreements, the University reserves the right to use results, data, information, etc. for, among other things, patient care purposes.

III.FINDER FEES AND BONUS PAYMENTS

Research sponsors typically provide financial support commensurate with the work required to do the study. Although some sponsors may offer to pay "finders' fees" or "bonus payments" to encourage participant recruitment efforts, University policy prohibits payment to or receipt by U-M researchers, including staff and students, of these types of payments.

A "finder's fee" is compensation of any type (eg cash, cash equivalent, office or medical supplies, educational stipends, gift certificates, travel cost in excess of normal reimbursement costs, or anything else of value) made to study team members in exchange for referral or recruitment of a participant to a research study (eg $10 for every person recruited who signs the consent document to participate in the study).

"Bonus payment" is defined here as compensation tied to the rate or timing of recruitment or performance or other aspects of a clinical study. Examples of bonus payments include the following: the sponsor announces that the highest enrolling site in the nation will receive a $10,000 bonus; the sponsor offers to pay an additional $10,000 beyond the budgeted study costs to any site than enrolls five participants within a week; the sponsor offers to pay an additional $10,000 beyond the budgeted study costs to any site that fulfills its recruitment target by the end of the month; the sponsor offers to pay an additional $1,000 beyond the budgeted study costs for any participant who agrees to enroll within one day of initial contact. It is not permissible to accept bonus payments at U-M.

The policy prohibiting "finders' fees" and "bonus payments" does not prohibit renegotiation of contract fees when recruitment is progressing much more slowly than anticipated such that additional time and effort are required for recruitment activities than initially anticipated. The policy also does not prohibit compensation for recruitment and screening related activities that are unrelated to whether the participant ultimately enrolls in or completes the research study (eg advertising, administrative, and personnel costs) or for the cost of services provided to those individuals who ultimately do enroll. (This policy does not address payments to research participants, which are addressed in Part 7. V).

Researchers should determine a reasonable budget amount that is directly related to the value of the services provided to the study and document how that amount was determined. Further, any payments to the University for personnel must be reflected in the study budget and in the written agreement that is reviewed by ORSP.

IV.ADDITIONAL INFORMATION

There are numerous applicable and helpful University web sites that provide information concerning University policies, Regental bylaws, and contracting procedures and requirements. Below are just a few of the links to such resources:

A. General Contracting Principles

- ORSP: Working with a Private Team Sponsor

B. Human Use in Research

- SPG 303.05 - Policy for Research with Human Participants
- U-M Federalwide Assurance of Protection for Human Subjects

PART 11: Laws, Regulations, and Standards

Describes selected laws and regulations commonly impacting human subjects research conducted at the U-M by faculty, staff, students and other trainees.

I. FEDERAL, LAWS, REGULATIONS, AND REQUIREMENTS COMMONLY APPLICABLE TO RESEARCH

Numerous laws, regulations, formal and informal guidance documents, and other standards govern research activities. These requirements are implemented by government bodies (eg federal or state government), federal agencies (eg HHS), or other national or international institutions (eg International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). These bodies may regulate the same or similar activities, which can result in conflicting guidance. Researchers must generally comply with the most conservative requirements.

A. Federal Laws and Regulations Applicable to Research

A brief outline of federal laws applicable to research is provided below, other standards may also apply.

1. The "Common Rule"

The Federal Policy for the Protection of Human Subjects is known as the "Common Rule" because it has been adopted by a number of federal departments and agencies. HHS maintains a list of federal agencies that have adopted the Common Rule: Federal Policy for the Protection of Human Subjects ('Common Rule').

The Common Rule requirements are integrated throughout this OM as well as in the standard operating procedures of the University's IRBs and other review units.

Absent an interpretation from the sponsoring agency to the contrary, the guidance provided by the HHS and the requirements of all of the subparts of 45 CFR 46apply to University research supported by Common Rule agencies. Further 45 CFR 46 includes several subparts that impose additional protections for identified vulnerable populations specifically, pregnant women, fetuses, and neonates (45 CFR 46 Subpart B); prisoners (45 CFR 46 Subpart C); and children (45 CFR 46 Subpart D). Many agencies have not adopted Subparts B, C, or D; unless the agency provides guidance to the contrary, however, the University interprets the subparts to apply to all federally supported University research.

For research that is not federally supported, and in accordance with the University's Federalwide Assurance (FWA) with the OHRP, the University adheres to equivalent protections that are consistent with the requirements of 45 CFR 46 and the subparts, but that allow flexibility in IRB review of these projects.

2. Clinical Trials Disclosure Requirements

The Food and Drug Administration Modernization Act (FDAMA), the Food and Drug Administration Amendments Act (FDAAA), and NIH policy mandate public registration of certain types of clinical trials. Failure to comply with these legal and policy requirements may result in administrative sanctions and civil penalties and, when applicable, withholding or even possible repayment of NIH funding.

Additionally, journals increasingly refuse to publish results of trials that were not adequately registered in a comparable registry prior to enrollment of the first participant. The International Committee of Medical Journal Editors (ICMJE)generally requires registration of research projects that prospectively assign human subjects to intervention and comparison groups in order to study the cause-and-effect relationship between a medical intervention (eg drug, surgical procedure, device, behavioral treatment, process-of-care change) and a health

outcome (broadly defined, including pharmacokinetics).

Private funders may also have ClinicalTrials.gov related requirements that need to be followed as well. Researchers conducting clinical trials subject to these requirements must identify the individual or entity that will act as the Responsible Party for registration and results reporting. Under the federal regulations (42 CFR 11), the Sponsor, meaning the person or entity responsible for initiating the trial and for control of the protocol, is considered the Responsible Party unless that responsibility is designated to a principal investigator (PI). At the University of Michigan, for investigator-initiated research, the PI is expected to take on the role of the Responsible Party, with two exceptions:

- If there is an IND or IDE held by someone other than the PI, the IND or IDE holder is the Responsible Party, and
- Within the Oncology CTSU, the UMRCC may retain Responsible Party status or may designate it to the Principal Investigator.

Per FDAAA, 42 CFR §11, and NIH policy the Responsible Party is required to:

- Register clinical trials information on ClinicalTrials.gov within the required time-frame,
- Ensure that informed consent documents contain the applicable language related to clinical trials registration,
- Maintain the ClinicalTrials.gov record by making required updates to the record, and
- Report results, generally, within one year of the primary completion date.

3. Certificates of Confidentiality

a. Generally

Certificates of Confidentiality (CoCs) are issued by the NIH, the Centers for Disease Control and Prevention (CDC), the FDA, the Substance Abuse and Mental Health Services Administration (SAMHSA), and the Health Resources and Services Administration (HRSA). CoCs protect the privacy of research participants by allowing investigators and institutions to avoid compulsory release of information that could be used to directly or indirectly identify individuals participating in a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted. When research is covered by a Certificate of Confidentiality, the researcher:

- May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.

Generally, either any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under an approved FWA issued by the OHRP or the approval of the FDA is eligible for a CoC. Information is considered sensitive if disclosing it could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

Information is considered identifiable if an individual is identified or there is at least a very small risk, that

some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

Usually, CoCs are issued for single, well-defined research projects following IRB approval. They may, however, be issued for cooperative multi-site projects under limited circumstances.

COCs are issued with expiration dates, but may be extended if the research continues past those dates. The protection afforded by a CoC is in any event permanent; all personally identifiable information maintained about subjects in the study while the COC is in effect is protected forever. Note, that if the CoC expires and the researcher continues to collect data from existing participants or enrolls new participants without formally extending the CoC, the data collected after the expiration date is not protected.

NIH provides CoCs automatically to any NIH-funded recipients conducting research involving identifiable, sensitive information. Examples of research automatically covered by a CoC include:

- Biomedical, behavioral, clinical or other research, including exempt research, except where the information obtained is recorded in such a manner that human participants cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
- The collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
- The generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained.
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

A project may receive protection under a CoC if the project is not sponsored or funded by NIH, as long as, in NIH's view, the subject matter of the study falls within a mission area of the NIH, including its Institutes, Centers, and the National Library of Medicine.

The CDC, FDA, SAMHSA, and HRSA only issue CoCs for research they sponsor.

b. Principal Investigator Responsibilities

Researchers conducting NIH-supported research covered by a CoC must ensure that if identifiable, sensitive information is provided to other researchers or organizations, regardless of whether or not the research is federally funded, the other researcher or organization must comply with applicable requirements when research is covered by a CoC. In addition, for NIH, CDC, and FDA issued CoCs, the protections from the CoC flow down to collaborators who have a sub-award or sub-contract if the collaborators' research activities are funded from those agency funds.

The existence of a CoC, the protection it provides, and any limitations on that protection should be described in the informed consent document:

- For studies that were previously issued a CoC, and notified participants of the protections provided by that CoC, NIH does not expect participants to be notified that the protections afforded by the CoC have changed, although IRBs may determine whether it is appropriate to inform participants

- If part of the study cohort was recruited prior to issuance of the CoC, but are no longer actively participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a CoC, to be notified that the protections afforded by the CoC have changed, or that participants who were previously consented to be re-contacted to be informed of the CoC, although IRBs may determine whether it is appropriate to inform participants.

Refer to U-M IRB informed consent templates for CoC language.

c. Disclosure

Certain disclosures are permitted even when a CoC has been issued. Disclosures are allowed if:

- Required by Federal, State, or local laws (eg as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

The IO or his designee must sign the statement of CoC assurances before submission to NIH, FDA, HSRA, SAMHSA, or CDC.

For information on how to apply for a CoC and other guidance, refer to U-M Guidance on Certificates of Confidentially.

For additional information about CoCs, see:

- NIH Certificates of Confidentiality
- FDA
- CDC
- HSRA
- SAMHSA

4. The Health Insurance Portability and Accountability Act (HIPAA)

The U.S. Department of Health and Human Services, Office for Civil Rights (OCR) has issued privacy and security regulations under the Health Insurance Portability and Accountability Act of 1996 . These regulations protect against unauthorized use and disclosure of individually identifiable information created or received by health plans, health care clearinghouses, and most health care providers ("covered entities"). Components of the University that are covered entities and therefore directly regulated by HIPAA include:

- U-M Health System Hospitals & Health Centers (including the U-M Medical School);
- IU-M Group Health Plans;
- Mary A. Rackham Institute (University Center for the Child and Family, University Center for Language and Literacy, and the Adult Psychological Clinic);
- School of Dentistry Provider Clinics; and
- University Health Service.

In general, a covered entity may allow protected health information under its control to be used or disclosed for

research only with an individual's written authorization. This authorization is described in 45 CFR 164.508. To be valid, the authorization must include at least the following information:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful way;
- The names or other identification of the specific people or categories of people (eg "your primary care physician" or "your health care providers") who can make the use or disclosure;
- The names or other identification of the specific people or categories of people who may receive the information (eg "the U-M," "the researchers," "the IRB and other University officials," "study sponsors," "government oversight agencies");
- A description of each purpose of the authorized disclosure (eg "to conduct the study," "to analyze any adverse reactions to the study intervention," "for study oversight,");
- An expiration date (eg January 1, 2016) or expiration event (eg "one year from signing" or "at the end of the study" or "none");
- Signature of the individual (or the person's legally authorized representative) and date;
- A statement of the individual's right to revoke his or her authorization in writing and any exceptions to that right;
- Whether treatment or payment will be conditioned on granting the authorization; and
- The potential for the information used or disclosed for the research to be redisclosed and no longer protected by HIPAA.

This authorization must be written in plain language. This information may be incorporated into a research consent form or provided separately to prospective subjects, depending on the requirements of the IRB overseeing the research. U-M standard informed consent templates incorporate the requirements for HIPAA authorization. In limited cases (described in 45 CFR 164.512), an IRB or Privacy Board may waive these authorization requirements. See this OM Part 3 for waiver criteria.

5. The Genetic Information Nondiscrimination Act (GINA)

GINA is a Federal law that prohibits discrimination in health coverage and employment based on genetic information. GINA, together with the nondiscrimination provisions of the Health Insurance Portability and Accountability Act (HIPAA), generally prohibit health insurers or health plan administrators from requesting or requiring genetic information of an individual or an individual's family members, or using such information for decisions regarding coverage, rates, or preexisting conditions. GINA also prohibits most employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment.

Since GINA has implications regarding the actual or perceived risks of genetic research and an individual's willingness to participate in such research, OHRP has provided guidance for investigators and IRBs so that they are aware of the protections provided by GINA as well as the limitations in the law's scope and effect. IRBs should consider the provisions of GINA when assessing whether genetic research satisfies the criteria required for IRB approval of research, particularly whether the risks are minimized and reasonable in relation to anticipated benefits and whether there are adequate provisions in place to protect the privacy of subjects and maintain the confidentiality of their data.

GINA is also relevant to informed consent. When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider whether and how the protections provided by GINA should be reflected in the consent document's description of risks and provisions for assuring the confidentiality of the data.

6. Substance Abuse Treatment (42 CFR 2)

Federal law imposes restrictions upon the disclosure and use of alcohol and drug abuse patient records that are maintained in connection with the performance of any federally assisted alcohol and drug abuse treatment program (a "Part 2 Program"). These regulations prohibit the disclosure and use of patient records unless certain circumstances exist. If a patient consents to a disclosure of his/her records, a Part 2 Program may disclose his records in accordance with that consent to any individual or organization named in the consent. The consent must include the following nine elements:

- The specific name or general designation of the program or person permitted to make the disclosure;
- The name or title of the individual, or name of the organization, to whom the disclosure is to be made;
- The name of the patient;
- The purpose of the disclosure;
- How much and what kind of information is to be disclosed;
- The patient signature (or signature of legally authorized representative);
- The date of signature;
- A statement that authorization may be revoked at any time except to the extent it already has been relied on to make a disclosure; and
- The date, event, or condition upon which authorization will expire if not revoked (the authorization may not last longer than reasonably necessary to serve the purpose for which it is given).

Further, per federal law (42 CFR 2.52), patient-identifying information may be disclosed for the purpose of conducting scientific research if certain requirements are met, as determined by the Part 2 Program Director:

- If the recipient of the patient identifying information is a HIPAA covered entity or business associate, it must have obtained and documented authorization from the patient, or a waiver or alteration of authorization, consistent with HIPAA; or
- If the recipient of the patient identifying information is subject to HHS regulations regarding protection of human subjects (45 CFR 46), it must either provide documentation that the researcher is in compliance with the requirements of the HHS regulations, including the requirements related to informed consent or a waiver of consent or that the research qualifies for exemption under the HSS regulations.
- If the recipient of the patient identifying information is both a HIPAA covered entity or a business associate and subject to the HHS regulations regarding protection of human subjects, both requirements above apply.
- If the recipient of the patient identifying information is neither a HIPAA covered entity or business associate and subject to the HHS regulations, this provision does not apply.

Additional obligations and restrictions apply to researchers using patient identifying information obtained pursuant to 42 CFR 2.52, including restrictions on re-disclosure and security procedures.

Furthermore, additional restrictions and obligations apply if researchers seek to link data sets or establish data repositories containing personally identifiable information from a Part 2 Program, including ensuring that patient identifying information is not provided to law enforcement agencies or officials.

B. Federal Agencies and Additional Federal Requirements Applicable to Research

Several federal agencies conduct or support human research. A number of these federal agencies have created additional, agency-specific regulations for the research they support. Each IRB is responsible for ensuring that investigators and research staff meet these additional regulations when conducting human research supported by a particular agency. In addition, U-M researchers are responsible for complying with additional regulations when

conducting human research supported by a particular agency.

An outline of federal agencies, as well as an overview of the laws and standards they oversee, is provided below.

1. Department of Health and Human Services

HHS and its various offices and operating divisions regulate human research supported with HHS federal funds or involving the use of investigational drugs, biologics, and devices. An overview of some of these offices/divisions and the laws these organizations oversee is provided below.

a. Office for Human Research Protections

The OHRP is part of the Office for the Assistant Secretary of Health under HHS. The OHRP provides guidance and regulatory oversight of biomedical and social-behavioral research in order to protect the rights, welfare, and well-being of human research participants. OHRP has oversight of the Common Rule and additional rules for research involving pregnant women, fetuses, and neonates (45 CFR 46 Subpart B); prisoners (45 CFR 46 Subpart C); and children (45 CFR 46 Subpart D).

U-M maintains an FWA with HHS. Refer to Part 1 of this OM for additional information.

b. Food and Drug Administration

The U.S. Food and Drug Administration enforces the FD&C Act and associated regulations, including regulations covering human subjects protections (21 CFR part 50), IRBs (21 CFR part 56), investigational drugs (21 CFR part 312), biologics (21 CFR 312 and 21 CFR subchapter F), and investigational devices (21 CFR part 812). Additional information about and requirements for research regulated by the FDA is provided in Part 8 of this OM and directly from the FDA.

c. National Institutes of Health, Office of Science Policy

The Office of Science Policy (OSP), through the Biosafety, Biosecurity, and Emerging Biotechnology Policy Division,) oversees research involving recombinant DNA (rDNA). OSP develops and implements NIH policies and procedures for the safe conduct of rDNA activities and human gene transfer (see The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules). Its duties include review and evaluation of the composition of institutional biosafety committees and development of registries of activities related to rDNA and human gene transfer research. OSP-regulated research is subject to oversight by the University's Institutional Biosafety Committee IBC.

d. Office of Research Integrity

The Office of Research Integrity (ORI) is located in the Office of the Assistant Secretary for Health under HSS. ORI promotes integrity in biomedical and behavioral research supported by the Public Health Service (PHS). ORI facilitates the responsible conduct of research through educational, preventive, and regulatory activities and monitors institutional investigations of research misconduct. ORI's response to misconduct depends on the circumstances, but may include government-wide debarment. ORI publishes all findings of misconduct. The University's local policy on research misconduct is described in the Standard Practice Guide 303.03. (See also the University's policy on integrity in scholarship.)

e. Office for Civil Rights

The Office for Civil Rights (OCR) is responsible for implementation and enforcement of privacy and security rules issued under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which protects individually identifiable health information (see 45 CFR 160 and 164). While the privacy and security rules do not directly regulate human research, they do govern the circumstances under which "covered entities" (health care providers, health plans, and health care clearinghouses) who control information necessary for many research activities may use, disclose, or provide access to that information. HIPAA is further discussed in Section I.A.4 of this part.

2. Department of Defense (DoD)
In addition to the Common Rule requirements adopted at 32 CFR Part 219, the DoD has additional requirements for human research it supports or conducts. See U-M HRPP Guidance: Additional Requirements for Department of Defense Sponsored Research.

3. Department of Justice (DOJ)
In addition to requirements adopted at 28 CFR 46, the DOJ has additional requirements for research conducted with the Bureau of Prisons and research involving the National Institute of Justice (NIJ). See U-M HRPP Guidance: Additional Requirements for Research Supported by the Department of Justice.

4. Environmental Protection Agency (EPA)
In addition to the Common Rule requirements adopted at 40 CFR 26, the EPA has additional requirements for human research it supports or conducts or for research that is otherwise intended for submission to the EPA. See U-M HRPP Guidance: Additional Requirements for Research Supported by the Environmental Protection Agency (EPA).

5. Department of Education (ED)
In addition to the Common Rule requirements adopted at 34 CFR 97, the ED has additional requirements for human research involving students or education records conducted at institutions receiving ED funding. These additional requirements include the FERPA (34 CFR 99) and the Protection of Pupil Rights Amendment (PPRA) (34 CFR 98).

The U-M IRBs may provide guidance regarding complying with PPRA and/or FERPA requirements, but the school providing access to its students or student records for research purposes is responsible for ensuring compliance with FERPA or PPRA. See U-M HRPP Guidance: Additional Requirements for Research Supported by the Department of Education (ED).

6. Department of Energy (DOE)
In addition to the Common Rule requirements adopted at 10 CFR 745, the DOE has additional requirements for human research it supports or conducts. See U-M HRPP Guidance: Additional Requirements for Research Supported by the DOE.

II. STATE LAWS, REGULATIONS, AND REQUIREMENTS COMMONLY APPLICABLE TO HUMAN RESEARCH

Studies conducted at the University or other in-state locations are subject to the laws and regulations of the State of Michigan. Studies performed in whole or in part in other states may be subject to different requirements. For example, different states may have different requirements for informed consent; confidentiality, privacy, and security standards; public health reporting mandates; limitations on participation of vulnerable populations in research; professional licensing requirements; etc. For human research conducted out-of-state, researchers are expected to comply with the requirements of those other states. Typically, University IRBs rely on local IRB or ethics board oversight to assure project compliance with local laws and regulations. Where the design of the research does not anticipate local review, PI may contact the U-M Office of the Vice President and General Counsel to determine whether the protocol is likely to implicate state laws that are inconsistent with those of Michigan. Note that it may be necessary for OGC to consult with external legal counsel in such situations, which could entail additional expense for the researcher.

Contracts signed with sponsors and funders of research and with research performance sites may also impose further restrictions. The PI is responsible for assuring that the study complies with all of these requirements.

This section describes legal standards under Michigan law only. Researchers are required to determine the laws and

standards applicable to their projects and follow them accordingly. Researchers may contact the U-M Office of the Vice President and General Counsel for general assistance in determining which laws and standards may be applicable to their project.

A. Informed Consent and Legally Authorized Representatives

Consent is addressed in Parts 3, 6, and 7 of this OM. This section contains a general overview of Michigan laws regarding informed consent that may be applicable to research. = Michigan requirements regarding consent are largely consistent with federal law.

1. Who May Give Consent

Competent adults (those able to understand the nature and consequences of their actions) must consent on their own behalf to participate in research. Children and adults with diminished capacity, however, are considered vulnerable and susceptible to coercion and undue influence. In general, neither of those groups may provide legally effective informed consent.

a. Children

Michigan law (MCL 722.1) defines the "age of majority" as an individual who is eighteen or older. Parents or legal guardians (as defined by MCL 700.5201-700.5219) must consent on behalf of children who are younger than eighteen.

The following exceptions to parental consent are allowed under Michigan law and the IRB will determine the applicability of these exceptions in the research setting:

- Emancipated minors (generally those who are validly married or are on *active duty* in the United States armed forces) (MCL 722.4e(1)(g));
- Children seeking confidential prenatal and pregnancy-related care (excluding abortions) (MCL 333.9132);
- Children age 14 and above seeking confidential limited outpatient mental health services (MCL 330.1707);
- Children seeking confidential substance abuse treatment (MCL 330.1264); and
- Children seeking confidential treatment for sexually transmitted diseases, including HIV/AIDS (MCL 333.5127).

b. Adults with Cognitive Impairment or Otherwise Impaired Decision-making Capacity

Federal law requires that a legally authorized representative consent to research participation on behalf of adults with cognitive impairment or otherwise impaired decision-making capacity. Under Michigan law, individuals who constitute a legally authorized representative are listed as follows, in descending order of priority:

- Patient Advocate named in a Durable Power of Attorney
- Guardian
- Spouse
- Adult child(ren)
- Parent(s)
- Adult sibling(s)

Michigan law (MCL 700.1105) defines an "incapacitated individual" as one "who is impaired by reason of mental illness, mental deficiency, physical illness or disability, chronic use of drugs, chronic intoxication, or other cause, not including minority, to the extent of lacking sufficient understanding or capacity to make

or communicate informed decisions."

For additional guidance, refer to the Office of the Vice President and General Counsel Consent FAQs. General Counsel can also assist with making determinations related to legally authorized representative issues.

2. Michigan Laws Requiring Special Consent

Michigan has adopted laws and regulations imposing specific consent requirements for certain types of clinical activities that may impact research. Principal Investigators are responsible for obtaining and documenting informed consent in compliance with applicable federal and state laws and institutional policies.

a. Electroconvulsive Therapy (ECT) (MCL 330.1717)

Michigan law outlines specific requirements prior to administration of ECT (or any procedure intended to produce convulsions or coma). Depending on circumstances, these requirements may include concurrence by two psychiatrists (neither of whom may be the treating psychiatrist), notice to the patient of his/her right to object, and/or potential a petition to probate court.

A U-M investigator who wishes to conduct clinical research that involves ECT should consult with the IRB and the Office of the Vice President and General Counsel to ensure compliance with state and federal laws.

b. Genetic Testing (MCL 333.17020 and 333.17520)

MCL 333.17020 and 333.17520 do not apply to procedures performed as a component of biomedical research subject to FDA and OHRP oversight. However, they do establish best practice in Michigan and should be followed when appropriate in the context of an individual research project.

Best practices in Michigan: a physician or other provider may perform a pre-symptomatic or predictive genetic test only after obtaining specific, written informed consent from the patient or patient's legally authorized representative. The informed consent must confirm that the physician or provider has explained, and the patient or his legally authorized representative understands, all of the following, at a minimum:

- The nature and purpose of the genetic test;
- The effectiveness and limitations of the genetic test;
- The implications of taking the genetic test, including, but not limited to, the medical risks and benefits;
- The future uses of the sample taken from the test subject in order to conduct the genetic test and the information obtained from the genetic test;
- The meaning of the genetic test results and the procedure for providing notice of the results to the patient; and
- Who will have access to the sample taken from the patient in order to conduct the genetic test and the information obtained from the genetic test, and the patient's right to confidential treatment of the sample and the information.

A copy of the informed consent form should be provided to the person who signed it. The original form, signed by the patient or his legally authorized representative, must be placed in the patient's medical record. The Michigan Department of Community Health (MDCH) has developed a patient information brochure and model informed consent document that it recommends for use with genetic testing.

c. HIV Testing (MCL 333.5133)

Michigan law has specific requirements related to informed consent for HIV testing. However, if the HIV test is performed solely for research purposes and if the test is performed in such a manner that the identity

of the test subject is not revealed to the researcher and the test results are not made known to the test subject, the requirements under Michigan law may not apply. The researcher still has the obligation to obtain informed consent as outlined in Part 6 of this OM.

If the researcher will know the identity of the subject and the test results are made known to the subject, then Michigan law requires the physician to do the following prior to the HIV test:

- Inform the subject or his or her legally authorized representative (LAR) verbally or in writing that an HIV test will be performed unless the subject or his or her LAR declines the HIV test.
- Offer the subject or his or her LAR an opportunity to ask questions and decline the HIV test. If the subject or his or her LAR declines the HIV test, the decision must be documented in the subject's medical record.

Under Michigan law, if the HIV test is positive then the health facility must provide post-HIV-test counseling to the subject and referrals to expedite HIV treatment and services.

Note that Michigan law does not require separate consent for HIV testing, an individual that provides general informed consent for medical care is considered to have consented to an HIV test.

Separately, the OHRP has published guidelines for AIDS research.

d. Pregnancy Termination (MCL 333.17015)

Michigan has enacted various laws related to pregnancy termination. Michigan mandates that a physician obtain written informed consent prior to the procedure, which must be given freely and without coercion. The physician must also provide certain information at least 24 hours before performing the abortion. The state-approved materials with this information are located on the MDCH web site. In the case of a minor seeking an abortion, the physician must also obtain written consent from one parent or the legal guardian of the minor unless such consent is waived by a court.

A U-M investigator who wishes to conduct clinical research that involves pregnancy termination should consult with the IRB and the Office of the Vice President and General Counsel to ensure compliance with state and federal laws.

B. Confidentiality of and Access to Research Records and Other Information

1. General Research Records

The "Confidential Research and Investment Information Act," MCL 390.1551-390.1557, exempts from disclosure under the Michigan Freedom of Information Act (FOIA, MCL 15.231-MCL 15.246) intellectual property created by individuals employed or contracted by the University for research, education, and related activities until a reasonable opportunity has been provided to publish. In addition, the Act protects from disclosure confidential information received by the University from third parties for research, education, and related activities, provided that the information is designated as confidential before it is received by the University, the University and the third party enter into an agreement to keep the information confidential, and other conditions are met. The law also protects copyrightable and patentable information, until a reasonable opportunity has been provided to obtain a copyright or patent.

In addition to the federal privacy and confidentiality standards, Michigan law (MCL 333.20201) generally provides that patients are entitled to the privacy of their medical information and prohibits hospitals and other health facilities from providing copies of patient medical records to third parties without prior authorization. Patients may refuse the release of their records outside a health facility except as required for transfer to

another health facility, as required by law or third party payment contract, or as permitted by HIPAA.

2. Information Pertaining to HIV/AIDS (MCL 333.5131)

All reports, records, and data pertaining to testing, care, treatment, reporting, and research, and information pertaining to partner notification under MCL 333.5114a, that are associated with infections of HIV infection and acquired immunodeficiency syndrome (AIDS) are confidential and can only be released pursuant to Michigan law.

Per Michigan law, the disclosure of information pertaining to HIV infection or AIDS is allowed in the following situations:

- In response to a court order, but only if (1) the court determines that other ways of obtaining the information are not available or would not be effective; and (2) the public interest in and need for the disclosure outweigh the potential for injury to the patient. The court order must: limit disclosure to those parts of the patient's record that are determined to be essential to fulfill the objective of the order; limit disclosure to those individuals whose need for the information is the basis of the order; and include other measures necessary to limit disclosure for the protection of the patient.
- To the Michigan Department of Community Health, a local health department, or other health care provider (1) to protect the health of an individual; (2) to prevent further transmission of HIV; (3) to diagnose and care for a patient.
- By a physician or local health officer to a known contact of the individual who is HIV infected or has been diagnosed as having acquired AIDS, if the physician or local health officer determines that disclosure is necessary to prevent a reasonably foreseeable risk of further transmission of HIV. (In this case, the physician or local health official has a duty to disclose the information to the known contact or to refer the individual who is HIV infected or has been diagnosed as having AIDS to a local health department for assistance with partner notification. The referral shall include available contact information for known contacts of this individual.) To the extent released, the information should not identify the individual to whom the information pertains unless reasonably necessary to prevent a foreseeable risk of transmission.
- If the disclosure is expressly authorized in writing by the individual who is HIV infected or has been diagnosed as having acquired AIDS. Written authorization must be specific to HIV infection or acquired immunodeficiency syndrome a minor or incapacitated, written authorization may be executed by the parent or legal guardian of the individual.
- As otherwise required or permitted by Michigan law.

3. Mental Health Treatment (MCL 330.1748)

Michigan law accords special protection to the privacy of mental health records. Mental health information may be disclosed as necessary for outside research, evaluation, accreditation, or statistical compilation. In this case, the individual subject should not be identified in the disclosed data set unless the identification is essential to achieve the purpose for which the information is sought or if preventing the identification would clearly be impractical. Under no circumstances may the information be disclosed if the subject is likely to be harmed by the identification.

In general, information in the record of a recipient of mental health services must be kept confidential and only may be disclosed with specific authorization of the recipient, with the following exceptions:

- If the recipient is a child, the authorization may be granted by the recipient's parent with legal custody.
- If the recipient is an incompetent adult, authorization may be granted by the recipient's legal guardian.
- If the recipient is deceased, the authorization may be granted by the personal representative or executor of the estate.

The law also significantly restricts any re-disclosure. Even when information is disclosed in accordance with Michigan law, the identity of the person to whom it pertains should be protected whenever feasible.

4. Substance Abuse Treatment (42 CFR 2; MCL 330.1260-330.1287**)**
Per Michigan law, substance abuse diagnosis, prognosis, and treatment records are confidential and may be disclosed only with consent of the individual to whom the record pertains unless one of the following applies:

- To medical personnel, to the extent necessary to meet a bona fide medical emergency;
- To qualified personnel, for the purpose of conducting scientific statistical research, financial audits, or program evaluation, but the personnel shall not directly or indirectly identify an individual in a report of the research audit or evaluation or otherwise disclose an identity in any manner; or
- By court order, as described in MCL 330.1263.

The individual may withdraw consent at any time unless prohibited by federal law.

C. Mandatory Disclosure Requirements

Various Michigan laws require U-M personnel to report information that might otherwise be considered confidential. Researchers are responsible for complying with the laws of other states, when applicable.

1. Michigan Freedom of Information Act
The Michigan FOIA (MCL 15.231-15.246) requires "public bodies" including the U-M to allow people to inspect, copy, or receive copies of "public records." A public record is defined as "a writing prepared, owned, used, in the possession of, or retained by a public body in the performance of an official function, from the time it is created." Most records created by University faculty, staff, and trainees in the performance of their University functions, or retained on University property or in University electronic resources, are public records subject to disclosure under FOIA. However, under FOIA, the institution must deny requests for a number of specific reasons, including student education records subject to the protections of FERPA. The Michigan FOIA also permits withholding of health records subject to HIPAA protections. In addition, the Confidential Research and Investment Information Act (CRIIA)(MCLA 390.1551-1557) offers some exemptions from disclosure for some sensitive materials provided by research partners and sponsors. (And of course, if research records protected by a Certificate of Confidentiality are requested under FOIA, the researcher should consult with HRPP and OGC about how to proceed to protect the records from disclosure.)

2. Mandatory Reporting Abuse, Neglect, and Violence
Michigan has enacted laws designed to protect children and vulnerable adults from harm by requiring various professionals to report suspected abuse or neglect.

The following is a description of Michigan laws on mandatory abuse, neglect, and domestic violence reporting. When a researcher can reasonably anticipate that mandatory reporting requirements will be triggered during the course of a project (eg, where the researcher is a mandatory reporter and (i) members of these vulnerable populations are likely to be recruited to participate in the study or (ii) the researcher plans to explicitly question subjects about any history of abuse, neglect, or domestic violence), the informed consent discussion and document should include a description of the researcher's mandatory reporting obligations.

a. Child Abuse and Neglect (Michigan Child Protection Law MCL 722.621-722.638**)**
Physicians and other licensed healthcare professionals, social workers, school administrators, counselors, teachers, law enforcement officers, clergy members, and child care providers with reasonable cause to suspect child abuse or neglect are required to report their suspicions to Child Protective Services.

The Michigan Department of Human Services maintains a list of professions required to report suspected child abuse or neglect as well as reporting resources There are penalties for failing to make a mandatory report. Note that withholding consent for medical treatment for a child based on a parent's religious beliefs does not necessarily constitute abuse or neglect.

b. Vulnerable Adults (MCL 400.11a)

Individuals employed, licensed, registered, or certified to provide health care, educational, social welfare, mental health, or other human services; employees of agencies licensed to provide these services; law enforcement officers; and certain medical examiners who have reasonable cause to suspect that a vulnerable adult has been abused, neglected, or exploited are required to report their suspicions to the county department of social services of the county in which the abuse, neglect, or exploitation is suspected of having or believed to have occurred. The term "vulnerable adults" refers to individuals who are unable to protect themselves because of mental or physical impairment or because of advanced age. There are penalties for failing to make a mandatory report. The Michigan Department of Human Services maintains a list of professions required to report suspected vulnerable abuse or neglect as well as reporting resources.

c. The "Gun and Knife Law" (MCL 750.411)

Michigan law requires hospitals, pharmacies, and their managers to report immediately to law enforcement authorities any person brought to these facilities with a wound or other injury inflicted by means of a knife, gun, pistol, or other deadly weapon, or by other means of violence. It likewise requires physicians treating patients with these types of injuries to report. See Michigan Medicine Disclosure of PHI for Law Enforcement Purposes Policy, 01-04-313.

3. Court Orders and Subpoenas

A court order, administrative agency record request, or subpoena may be issued to require an institution (such as a hospital or university) or an individual (such as a researcher) to give testimony or to provide documents related to a case or other controversy. These documents may require release of confidential research records or clinical information. A University faculty, staff member, or trainee who receives a subpoena or court order related to University research should consult with the Office of the Vice President and General Counsel.

D. Additional Protections for Vulnerable Populations

1. Research Involving Prisoners and Other Detained Persons

Michigan law (Mich. Admin. Code R. 791.733) requires correctional facilities to implement policies to prohibit the use of inmates for "medical, pharmaceutical, or cosmetic experiments." This prohibition does not apply to individual treatment of an inmate based on the need for a specific medical procedure that is not generally available outside of the research. An IRB should not approve research that would be prohibited under this regulation, even if a particular facility has failed to implement the required policies.

Refer to Part 7 of this OM for additional information regarding research involving prisoners or other detained persons.

2. Research Involving Pregnant Women, Fetuses, and Neonates

Michigan law (MCL 333.2685-333.2691) prohibits use of a live human embryo, fetus, or neonate for non-therapeutic research if the research "substantially jeopardizes" its life or health, based on the judgment of the researcher and the available knowledge at the time of the research. Nontherapeutic research is any scientific or laboratory research or other kind of experimentation or investigation not designed to improve the health of the research subject. Nontherapeutic research is prohibited if the researcher is aware that the embryo or fetus is subject to a planned abortion being performed for any purpose other than to protect the life of the mother. This prohibition does not apply to any diagnostic, assessment, or treatment procedures performed on the fetus with

the purpose of either determining the life or status of the fetus or improving the health of either the fetus or the mother.

A dead embryo, fetus, or neonate is not considered a "human subject" for purposes of the HRPP. However, Michigan law (MCL 222.2688) permits research on a dead embryo, fetus, or neonate only if the mother grants express written consent. This research is to be performed in accordance with the same standards applicable to research conducted pursuant to the Uniform Anatomical Gift Law.

E. Stem Cell Research

In addition to the limitations on embryonic research described above, Michigan law (MCL 333.16274 and 750.430a) prohibits "human cloning," defined as "the use of human somatic cell nuclear transfer technology to produce a human embryo." "Human embryo" means a human egg cell with a full genetic composition capable of differentiating and maturing into a complete human being. "Human somatic cell" means a cell of a developing or fully developed human being that is not and will not become a sperm or egg cell. "Human somatic cell nuclear transfer" means transferring the nucleus of a human somatic cell into an egg cell from which the nucleus has been removed or rendered inert.

The Michigan Constitution (Article 1, Section 27) also describes conditions surrounding research involving human embryos. Generally, the Michigan Constitution permits any research that would be permitted under federal law with some additional limitations and requirements, including:

- No stem cells may be taken from a human embryo more than fourteen days after cell division begins (not including time during which an embryo is frozen);
- The human embryos were created for the purpose of fertility treatment and, with voluntary and informed consent, documented in writing, the person seeking fertility treatment chose to donate the embryos for research; and
- The embryos were in excess of the clinical need of the person seeking the fertility treatment and would otherwise be discarded unless they are used for research; or the embryos were not suitable for implantation and would otherwise be discarded unless they are used for research.
- No person may, for valuable consideration, purchase or sell human embryos for stem cell research or stem cell therapies and cures.

F. Document Control and Record Retention and Destruction

Document retention obligations may vary depending on the nature of the research and the academic unit with which the PI is affiliated. Generally, the most restrictive requirement applicable to a particular research record should be applied. Record retention requirements that may be applicable to research records include the following:

- For any clinical research or other research involving the collection or use of protected health information (i.e., information subject to HIPAA requirements), the general rule of thumb is that documents must be retained at least 7 years after the last intervention or interaction with subjects (45 CFR 164.528).
- For FDA-regulated research, records must be retained the longer of: (i) 7 years after the last intervention; or (ii) 2 years after approval of the drug or device or, if there is no approval, then 2 years after termination of the study with FDA (21 CFR 312.57).
- All federal grant-related administrative/financial records must be maintained at least 3 years following the end of the grant (or in the case of a repeating 5-year grant, 3 years following the end of the relevant segment) (2 CFR 200.333). Private sponsors may require longer periods and this can be determined only by reviewing the sponsorship agreements on a case-by-case basis.

- Michigan law (MCL 333.16213) requires that licensed health care providers maintain patient records for seven years after the date of service, unless a longer federal or state requirement applies. Note: UMHS Medical Record Retention Policy 03-09-008 requires retention of Medical Records for no less than 40 years.
- Because health care fraud and abuse laws allow the government to reach back up to 10 years (31 U.S.C. 3729), a 10-year retention period is recommended, but not mandated, where feasible for research that may be regulated by these laws.
- For other research, records should be retained for at least 3 years after termination of the study.

G. State Professional Licensing Laws and Institutional Credentialing Policies

Michigan laws limit who may practice in the various health professions, define the scope of practice of various types of licensees (eg doctors, nurses, dentists, psychologists, social workers, etc.), and describe whether and to what extent licensed professionals may delegate their functions to unlicensed individuals. Similarly, U-M credentialing and privileging policies and determinations restrict who may practice at U-M and the specific procedures or treatments they are authorized to perform.

Generally, investigators and research staff may not perform functions for clinical trials that they are not otherwise eligible to perform for non-research purposes. Specific state licensing laws should be consulted if there is any question as to the appropriateness of an individual's functions in the context of a research study. For questions pertaining to licensing issues regarding a research project, contact the Office of General Counsel. Note that it may be necessary for OGC to consult with external legal counsel in such situations, which could entail additional expense for the researcher.

III.INTERNATIONAL RESEARCH

The U-M facilitates the conduct of international human research by its faculty, students, and staff. International research frequently poses special concerns for IRBs and PIs to consider when evaluating risks and benefits to subjects and the appropriateness of study procedures. IRB SOPs must describe procedures for obtaining local IRB or ethics committee approval or must describe alternative procedures for seeking input on subject protection when an IRB or ethics board is not available or not necessary based on the research design. Additional requirements may be mandated by research sponsors, U.S. government agencies, and international agencies, depending on the specific location of the research and the nature of the study. The HHS Office of Human Research Protections maintains an online compilation of international laws and regulations pertaining to human research protections.

PIs are responsible for understanding and complying with the ethical and legal aspects of conducting human research in an international setting.

A. World Medical Association (WMA)

The World Medical Association (WMA) is an international organization created to ensure the independence of physicians. A central objective of the WMA is to establish and promote the highest possible standards of ethical behavior and care by physicians. In pursuit of this goal, the WMA has adopted global policy statements, many of which are recognized internationally as the global ethical standards for the topics they address, on a range of issues related to medical professionalism, patient care, research on human subjects, and public health.

One of the WMA's most important policy statements is the Declaration of Helsinki, which outlines ethical principles for medical research involving human subjects, including research on identifiable human material and data.

B. International Conference on Harmonisation Good Clinical Practice (ICH-GCP)

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting

clinical trials that involve human participants. Compliance with the standard provides public assurance that the rights, safety, and well-being of trial participants are protected; consistent with the principles of the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of the ICH-GCP Guideline (published in 1996) is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. ICH-GCP is not law in the United States, but has been adopted as guidance by the FDA.

A sponsor may require that a FDA-approved protocol and any investigator SOPs associated with that protocol would, if followed, assure ICH-GCP compliance.

If an investigator in the research contract agrees to conduct an investigation in full compliance with the investigator obligations under ICH-GCP, any compliance review conducted by the U-M ORCR will be done against the complete set of ICH-GCP requirements. Investigator obligations under ICH-GCP can be found in U-M HRPP Guidance: ICH-GCP.

C. The General Data Protection Regulation (GDPR)

GDPR is a data privacy regulation intended to protect the personal information of persons physically located within the European Union (EU). GDPR may apply to the collection of personal data during the conduct of a research project if the data is collected from an individual who is physically located within the EU at the time of data collection. GDPR may also apply to the transfer of personal data originally collected under GDPR from an EU country to a non-EU country. U-M researchers should consult with the IRB to determine if GDPR applies to a particular research project. Additional information regarding U-M and GDPR compliance can be found on the U-M Safe Computing Website.

IV.ACCESS TO LEGAL COUNSEL

Members and staff of IRBs and other review units, have access to legal advice concerning application of the laws and regulations that affect human research through the U-M's Office of the Vice President and General Counsel.

PART 12: Quality Assurance, Quality Improvement, and Research Compliance

Describes the HRPP's quality assurance and quality improvement activities and objectives, reportable events, and research compliance oversight.

I. QUALITY ASSURANCE AND IMPROVEMENT

Quality assurance (QA) is an evaluation of whether or not activities meet defined standards. Quality improvement (QI) is a process initiated to improve a practice or procedure and to institutionalize the practice. QA/QI activities comprise a critical component of the HRPP and play a vital role in protecting the rights and welfare of research participants. They assist in the institutionalization of sound, ethical research design and procedures; promote compliance with laws, regulations and institutional policies governing the conduct of research; and are critical in the development of a culture that promotes and rewards ethical behavior.

A. Performance Measurement and Quality Assurance

The various University units and functions responsible for operation of the HRPP identify and communicate legal and regulatory standards and best practices applicable to human subjects research. These are reflected in and communicated throughout the University community the University's Standard Practice Guide 303.05, this Operations Manual, IRB Standard Operating Procedures, policies and procedures implemented at the individual unit level, mandatory educational modules, and a variety of *ad hoc* communications.

Performance measurement and quality assurance is an ongoing process and includes the following formal and informal activities:

- Initial and continuing IRB review and monitoring;
- Not-for-cause and for-cause audits;
- Continuing analysis of regulatory developments and sponsor standards, analysis of their application to University research, and integration as appropriate into the HRPP;
- Solicitation, review and analysis of research participant, researcher, HRPP staff, and other stakeholder feedback;
- Data collection and analysis to identify the cause and determine remediation of identified performance gaps;
- Development and implementation of corrective action plans in response to internal and external investigations and inspections;
- Receipt, investigation, and response to complaints;
- Risk assessment; and
- Accreditation.

B. Quality Improvement

Quality improvement occurs at all levels of the HRPP and includes the following activities:

- Education of the research community through in-person and online training, website development, and dissemination of formal and informal guidance;
- Policy development;

- Significant investment in technological improvements that facilitate workflow integration among and between HRPP entities and that provide "control points" for regulatory compliance; and
- Training and mentoring to provide qualified and experienced IRB staff and IRB membership, compliance and auditing staff, and research team personnel.

Effectiveness of the HRPP's quality improvement initiatives is measured both at the study level through post-approval-monitoring and at the system level through system-wide audits, accreditation, and other activities for evaluating the effectiveness of HRPP initiatives.

C. Research Compliance Review

To assist with both quality assurance and quality improvement activities the University established the Office of Research Compliance Review (ORCR). ORCR's mission is to facilitate safe, ethical, efficient, and high quality human research. ORCR activities include conducting compliance reviews of research studies, IRBs, and other HRPP components, participating in and leading various HRPP working groups, and coordinating accreditation efforts.

ORCR compliance reviews are divided broadly into routine and for-cause reviews and are described in the ORCR SOPs. Generally, ORCR activities are conducted according to a work plan that is developed annually and outlines compliance measures and objectives.

Through the various activities, ORCR conducts objective analysis and evaluation of research activity compliance for studies and for the HRPP as a whole. Outcomes of ORCR reviews inform quality assurance and drive systemic improvements.

In addition, ORCR issues an annual report that includes a summary of quality assurance activities and recommendations for quality improvement. Identified performance gaps and priorities for quality improvement are discussed at HRPP Advisory Council and other HRPP leadership meetings.

II. REPORTABLE EVENTS: ADVERSE EVENTS, UNANTICIPATED PROBLEMS, NONCOMPLIANCE, SUSPENSIONS, AND TERMINATIONS OF IRB APPROVAL

A. Background

It is a condition of the University of Michigan Federalwide Assurance of Protection for Human Subjects(FWA) that the institution have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the head (or designee) of any federal department or agency conducting or supporting the research, and any applicable regulatory bodies, including the HHS OHRP or the FDA for research subject to FDA oversight, of any:

- Unanticipated problems involving risks to research participants or others;
- Serious and/or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB(s); and
- Suspension or termination of IRB approval.

B. Definitions

1. Adverse Events (AEs)

OHRP defines an AE as "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research." Further, "adverse events encompass both physical and psychological harms.

They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research." (OHRP, *Unanticipated Problems Involving Risks & Adverse Events Guidance*, 2007)

In the context of multi-site studies, OHRP further defines internal and external AEs from the perspective of a particular engaged institution, where internal AEs are those AEs experienced by subjects enrolled by the researcher(s) at that institution, and external AEs are those AEs experienced by subjects enrolled by researcher(s) at other institutions engaged in the study.

The FDA defines an AE as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related." (21 CFR 312.32)

2. Unanticipated Problems (UAP)

OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

- It is "unexpected" in terms of its nature, severity, or frequency given 1) the research procedures described in the protocol-related documents, such as IRB-approved research protocol and informed consent documentation; and 2) the characteristics of the subject population being studied;
- It is "related" or "possibly related" to the participation in the research; meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- It suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (OHRP, *Unanticipated Problems Involving Risks & Adverse Events Guidance*, 2007)

The FDA indicates an AE observed during the conduct of a study should be considered an *unanticipated problem* involving risk to human subjects, and be reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study (eg requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. (FDA, Guidance for Clinical Investigators, Sponsors, and IRBs - Adverse Event Reporting to IRBs, 2009)

Although all unanticipated problems are either AEs or ORIOs, not all AEs and ORIOs are unanticipated problems.

3. Unanticipated Adverse Device Effect (UADE)

The FDA's IDE regulations define an UADE as "any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." (21 CFR 812.3(s)

4. Suspension

Suspension of an IRB approved protocol is when an approved protocol is partially or completely stopped by the IRB pending future action by the IRB or other regulatory entity in order to protect research participants. If the IRB is undertaking further inquiry, a voluntary "hold" during this fact-finding period does not constitute a suspension of IRB approval for purposes of the HRPP reporting to external agencies or sponsors.

5. Termination
Termination of an IRB approval is defined as a permanent halt in IRB approval of all research related activities as a result of direct action by the IRB. A request from a PI to terminate IRB approval at the end of a study's defined approval period, or at any other earlier point during the approval period, does not constitute a termination of IRB approval for the purposes of the HRPP reporting to external agencies or sponsors.

6. Noncompliance
The failure of a person or organization to act in accordance with the requirements of a law, regulation, policy, or the requirements and/or determination of an IRB.

7. Serious Noncompliance
Noncompliance that materially increases risks or causes substantive harm to research participants or materially compromises the rights or welfare of participants, including consideration of the following:

- Harm to participants;
- Exposure of participants to a significant risk of substantive harm;
- Compromised privacy and confidentiality of participants;
- Willful or knowing research misconduct on the part of the researcher;
- A violation of ethical principles for human research; or
- Damage caused to the scientific integrity of the data collected.

8. Continuing Noncompliance
Noncompliance that recurs after a researcher has been notified of a similar or related noncompliance concern pertaining to one or more protocols.

9. Allegation of Noncompliance
An unconfirmed report of noncompliance.

C. Roles and Responsibilities for Required Reporting of Reportable Event

This section outlines the general roles and responsibilities related to reportable events. Additional description of reporting procedures related to noncompliance is included in section III of this part.

1. Researchers
The PI of any research project is responsible for tracking, documenting, and reporting AEs and ORIOs, including self-identified noncompliance to the IRB overseeing that project, and must understand the nature and significance of unanticipated problems. PIs must follow IRB reporting guidelines. Information that must be reported to the IRB, along with the timelines for reporting, is posted on each IRB's website. All reportable information is submitted by researchers through the eRRM system for review by the IRB, and must include a detailed description of the events, the researchers assessment, any actions taken, and supporting documents.

In addition, PIs must forward to the IRB any inspection, audit, or investigation reports issued by internal or external sponsors or oversight authorities as required by IRB policies or by a study-specific reporting plan approved by the IRB. Key responsibilities of researchers are described in more detail in Part 6 of this manual.

2. The IRBs
IRBs must require, through SOPs or other policies or guidelines, the reporting of specified AEs and ORIOs in accordance with a defined process and timetable.

The IRB SOPs explain the timing and methods by which all reports submitted by researchers are reviewed.

Generally, IRB staff members conduct the initial review of a report to ensure completeness and to make a preliminary assessment of whether the report meets the OHRP's or FDA's definition of unanticipated problem (including those reports not characterized by the researcher or sponsor as an unanticipated problem), or when the report represents a serious, unexpected, and related adverse event. Reports of concern are forwarded for prompt review to an IRB member with expertise for assessment or to the IRB Chair, who may act on behalf of the IRB with regard to such a review.

The IRB Chair is authorized to take immediate action to protect the health and safety of research participants. Such action may take the form of: (i) asking the researcher to voluntarily impose a hold on the recruitment of participants to facilitate further inquiry by the IRB and/or institutional officials; (ii) asking the researcher to voluntarily impose a hold on the recruitment and research intervention to facilitate further inquiry by the IRB and/or institutional officials; (iii) suspending recruitment or enrollment; (iv) altering or suspending current interventions; or (v) terminating the IRB's approval of the project.

Any such action of the IRB chair will be documented in the IRB research record immediately. If the IRB chair imposes a partial or complete suspension, the IRB chair will promptly (ie no later than three business days) report the suspension to the HRPP Director. The IRB chair shall report any such action taken to the convened IRB at its next regularly scheduled meeting.

While the IRB is undertaking further inquiry, any voluntary "hold" during the fact-finding period does not constitute a suspension of IRB approval for purposes of the HRPP reporting to external agencies or sponsors.

A convened IRB will review reportable events occurring on studies under its direct oversight as well as reportable events that are potential UAPs (internal and external), potential serious adverse events, and potential serious and/or continuing noncompliance from studies that are otherwise reviewed via the expedited procedure. The IRB may endorse the interim action by the chair, if any, or may take a different action or additional actions. In the event immediate action is not required to protect the health and safety of research participants, any of the above actions must be approved in advance by a vote of the IRB.

3. Institution

If the IRB determines that a submitted report is a UAP, the IRB will follow the methods for prompt reporting described in their SOPs. Generally, required reports to federal agencies for unanticipated problems will be made promptly (ie not to exceed one month, absent special circumstances, such as the need for extensive data gathering or analysis).

If the IRB makes a determination of **suspension**, or **termination**, it will promptly (ie no later than three business days) inform the HRPP Director. The HRPP Director will promptly (ie not to exceed one month, absent special circumstances, such as the need for extensive data gathering or analysis) notify federal agencies and sponsors as required by regulations or agreements and provide notification to the IO, the IRB, the Associate Vice President for Research, the PI, and other institutional and external entities as needed. The following information will be included when making required reports to federal agencies:

- 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 awards (eg grants, contracts, or cooperative agreements);
- A detailed description of the problem; and
- Actions the University is taking or plans to take to address the problem (eg revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.)

Reports are shared with other sites involved in research, when appropriate.

III.COMPLIANCE OVERSIGHT

A. Background

The HRPP promotes an organizational culture that encourages a commitment to compliance with the legal, regulatory, and ethical principles that govern human research. The program relies on a system of self-regulation and integrated oversight to accomplish this objective. The IO strives to promote and enforce the program consistently throughout the organization and ensure its acceptance. This is achieved by maintaining the utmost respect for individuals, clearly communicating expected behaviors, fostering principled reasoning based on shared values, and recognizing shared responsibilities.

The following section describes the circumstances under which allegations of noncompliance may and must be reported and the process for reporting, the protections afforded individuals who make reports, and the process for investigating and responding to reports. Although all complaints and concerns related to the HRPP or to the conduct of individual studies are reviewed, they may not all involve noncompliance.

B. Noncompliance Review Procedures

1. Process Summary

Generally, reports of potential noncompliance related to specific research projects are first reviewed by the responsible IRB. IRBs may take interim actions as noted in their SOPs, including suspension of research to protect research participants while a concern is under review. Any suspension or termination of research is reported to the HRPP Director, so that the UMOR may make the required external reports. If, after initial review, the IRB decides that the report may represent serious and/or continuing noncompliance, it reports the case to the HRPP Director. The HRPP Director may conduct additional fact-finding using the resources of the Office of Research Compliance Review (ORCR) and additional faculty input as needed. When the IRB makes a final determination of serious and/or continuing noncompliance, it reports the determination to the HRPP Director, so that the HRPP Director may make the required external reports.

The review procedures described in this section are followed for all complaints or allegations of noncompliance including reports of attempts to exercise undue influence over IRB staff or member or HRPP administrator, described in Part 1.V. of this manual.

Complaints that are not related to a specific research project, may be directed to the IRB Chair or the HRPP director or the nearest organizational entity. All inquiries are taken seriously and are directed to the appropriate personnel, while following procedures to promote a fair and objective outcome.

2. Policy Against Retaliation for Reporting

Consistent with the requirements and spirit of the Michigan Whistleblowers Protection Act, a University employee may not be discharged, threatened, or otherwise discriminated against (with respect to compensation, terms, conditions, location or privileges of employment) because the employee made a report (or is preparing to make a report) of a violation or suspected violation of applicable human research laws or regulations, University policy, or IRB requirements, unless the employee knew the report was false or materially misleading. Any violation of this policy must be reported to the University. The University's Compliance Hotline is one option that permits confidentiality to be maintained.

C. How Compliance Concerns are Brought Forward

All researchers and research review units and their staff are responsible for maintaining the integrity of the HRPP. Accordingly, all are expected to report identified compliance concerns, including concerns of coercion or undue influence.

Complaints or allegations of noncompliance may be made by participants or their representatives, faculty, staff, or others engaged in research or responsible for related University oversight activities. Written informed consent documents provide a contact phone number that research participants or their representatives may call to discuss concerns or complaints regarding research studies. The University's HRPP web site and individual IRB websites also provides the telephone numbers and email contacts for IRB staff members and for the U-M Office of Research. In addition, the University provides anonymous reporting through the Compliance Hotline. As described in detail in Section D below, faculty and staff are obligated to report noncompliance concerns.

Allegations of noncompliance are normally reportable directly to the IRB with jurisdiction over the relevant research protocol but may be transmitted directly to the HRPP Director, the IO, ORCR, the Office for the Vice President and General Counsel, the Director of University Audits, the Compliance Hotline, or to other institutional officials (such as the appropriate dean, director, or department head). The recipient of any allegation, complaint, or other concern must forward this information to the IRB with jurisdiction over the study or studies. If the concern relates to the conduct of an HRPP subsystem that is not affiliated with a specific IRB, the concern should be forwarded to the HRPP Director. The IRB SOPs will contain, at a minimum, expected timeframes for addressing allegations of noncompliance and provisions for exceptions to these timeframes in extenuating circumstances.

Allegations of noncompliance may also emerge through internal or external audits by the IRBs or ORCR, or site visits or audits by regulatory agencies, such as FDA or research sponsors or their agents. If a complaint or allegation is received by any of these methods, it must be forwarded promptly to the responsible IRB for prompt initiation of established IRB-level review procedures. The HRPP Director will decide on the appropriate initial review location for concerns about noncompliance by the IRBs themselves or by other HRPP components.

Any complaint or concern identified by OHRP about human research conducted at or by the University will, in accordance with OHRP policy, be directed in the first instance to the IO. The HRPP Director is delegated primary responsibility for assuring appropriate internal investigation and response to any such report and will seek the assistance of the IRBs and ORCR in fulfilling this responsibility.

D. Receipt and Initial Handling of Allegations of Noncompliance

The IRB, through appropriate members and/or staff (and consistent with locally adopted SOPs, if any), will initiate a fact-finding review. The IRB Director determines whether the complaint or allegation of noncompliance is reportable immediately to the IRB Chair(s) for a determination of potential serious and/or continuing noncompliance. If the IRB Director concludes that the concern clearly is without merit or that the conduct in question (i) clearly does not constitute serious and/or continuing noncompliance; and/or (ii) can be addressed through minor corrective action agreed to by the PI or other involved parties, the matter may be appropriately addressed and closed.

Noncompliance that does not rise to the level of potentially serious or continuing is handled by the IRB following their SOPs. Sections E to H describe the process for handling noncompliance that is potentially serious or continuing.

E. Chair and Board Considerations and Determinations

Potential noncompliance, particularly if the conduct in question might constitute serious and/or continuing noncompliance, is referred to the IRB Chair(s) for additional review. The IRB Chair(s) must perform or make

arrangements for any additional fact finding necessary to make an initial determination. In reviewing the alleged noncompliance, the Chair(s) may request a meeting with the PI and others to discuss the allegations and provide an opportunity for the study team to answer any questions.

While the investigation is taking place, the Chair(s) may request a researcher to voluntarily "hold" new research participant accrual or research-related interventions during the fact-finding period, unless to do so would place participants at risk of immediate harm or otherwise jeopardize their course of treatment. Such a voluntary hold does not constitute a suspension of IRB approval for purposes of the HRPP reporting to external agencies or sponsors. A Chair, consultant, IRB member or staff person with an actual or apparent conflict of interest associated with the research or individual(s) that are the research participant of the concern must recuse him or herself from involvement in the matter.

After reviewing any relevant information gathered about the alleged noncompliance, the Chair(s) must make a preliminary assessment as to whether or not it has caused injury to a subject, represents an unanticipated problem involving risks to participants or others, or whether or not it constitutes potentially serious and/or continuing noncompliance with IRB determinations, applicable regulations, or HRPP policies. If the Chair(s) determines that the conduct does not represent serious or continuing noncompliance, the Chair(s) may determine the relevant parties to develop an appropriate corrective action plan.

If the Chair(s) determines that the conduct represents potentially serious and/or continuing noncompliance, the matter (together with sufficient background to facilitate an informed discussion and decision) must be referred to the convened IRB for review and discussion of the findings, recommendations regarding corrective actions (examples described below), and vote to approve the recommended actions. The convened IRB may request additional information for consideration before proceeding to a vote. The results of the convened IRB meeting will be provided to UMOR within one month, absent extenuating circumstances.

F. Actions of the HRPP Director as Delegated by the IO

When the HRPP Director receives a report from an IRB (or from another source regarding an issue outside a U-M IRB's jurisdiction), he or she will review the report and determine whether additional investigation is needed. If so, the HRPP Director will, directly or through a designee, conduct the investigation, or will require that one be completed through the relevant academic unit, research review unit, or the ORCR. Upon completion of such an investigation, a report must be drafted (with specific recommendations for corrective action, if merited) within a time specified by the HRPP Director. Upon receipt of the report, the HRPP Director together with the IO and in consultation, as appropriate, with the relevant IRB and other interested parties, may determine that no further action is needed; or may take any other action appropriate under the circumstances.

References to the HRPP Director in Part 12 of the Operations Manual also encompass any qualified individual designated in this role during the unavailability of the HRPP Director.

G. Response to Determinations of Noncompliance

Each IRB, as well as the IO and other institutional authorities, has the authority at any time to suspend or terminate approval of human research that is not being conducted in accordance with applicable laws and regulations, institutional policy, or an IRB's requirements, or that has been associated with unexpected serious harm to participants or others, or that for any other reason is believed to impose unreasonable risks on participants or others.

Other sanctions may be imposed in response to findings of noncompliance, depending on the severity and nature of the noncompliance. Examples include the following:

- Development and implementation of case-specific corrective action and mitigation plans;

- Protocol modification or termination;
- Modification of the continuing review schedule;
- Monitoring of the consent process;
- Notifications to or re-consenting of participants;
- Recommended or mandatory education or mentoring requirements;
- One-on-one mentoring;
- Regular or remedial IRB courses;
- Additional on-line training modules;
- Additional professional certification;
- Attendance at regional/national meetings/seminars;
- Increased monitoring or oversight; and
- Random or targeted audits.

The IO may institute any or all of the following additional sanctions:

- Embargo or destruction of research data;
- Refunding improperly billed/incurred costs;
- Notification to publishers with present or past submissions of circumstances of noncompliance and status of data;
- Faculty or staff suspension from engagement in University research; and
- Other disciplinary sanctions up to and including dismissal (in consultation, where required by University policy, with other appropriate institutional authorities and subject to any additional University due process requirements).

H. Institutional Notification and Reporting Requirements

In the event the IRB votes that the alleged noncompliance constitutes serious and/or continuing noncompliance, the IO must ensure the prompt reporting of this information to government authorities with jurisdiction and to sponsors to the extent required by any relevant regulations, grants, or contracts. In addition, reports are made to other entities including accrediting bodies as required. The HRPP Director will provide notification of external reporting to the IO, the IRB, the VPR, the PI, and other institutional entities as indicated.

Where the IRB votes determines that the alleged noncompliance is neither not serious and/or continuing, the IO may accept the IRB determination, may reject the determination and report externally as required, or conduct an additional investigation of the allegation.

Part 13: Education and Training

Describes educational resources available at the University and outreach activities to research participants and their communities.

I. EDUCATION IN GENERAL

The U-M and its faculty, staff, and trainees are committed to complying with the laws and regulations that govern the review and conduct of human research and to upholding the highest ethical standards. To help achieve this and ensure the protection of research participants, the University requires a basic level of human research protection education and provides a variety of educational activities designed to enhance the understanding of protection for research participants at all levels including leadership, IRB members and staff, researchers, research staff, and communities.

A. Required Education

U-M has developed an online Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) required for designated University faculty and staff, students, and collaborators involved in human research. PEERRS offers a Human Subjects Research Protections course that fulfills regulatory requirements for training in the protection of research participants in research. This course is modeled on the Collaborative Institutional Training Initiative (CITI) Human Subjects Research modules. Certification in the PEERRS course is granted for three years from the last date the user passes a certification test. Completion of this course is a requirement for IRB approval and is monitored through the IRB application.

GCP training is required for all researchers and research staff involved in the conduct, oversight, or management of NIH-funded clinical trials or specific studies conducted under GCP requirements. GCP training must be completed every three years or sooner if required for the conduct of a specific study.

In addition, individuals may be required to complete additional training depending on the scope and nature of the specific research. Additional information on training requirements and resources is available on the HRPP website.

II. HRPP LEADERSHIP TRACKING AND COMMUNICATING NEW DEVELOPMENTS

University officials responsible for regulatory compliance are made aware of new legal and policy developments through a variety of sources, which include: membership in professional associations; participation in and assumption of leadership roles with professional organizations; participation in relevant electronic listservs; access to electronic regulatory, legislative, and analytical resources; and attendance at regional and national educational conferences. Government Relations representatives keep regulatory compliance staff apprised of relevant pending legislation and regulatory activities, and the Office of the Vice President and General Counsel assists in providing analysis of these developments.

University officials in turn notify the research community of relevant developments through multiple mechanisms including: policy revisions; changes to application forms and guidelines; newsletters; educational sessions; web postings; and other communications, as necessary to promote ongoing compliance.

All of the individuals with a defined leadership role in the HRPP are linked to multiple nodes in the system. For example, the DIO has roles on the Conflict of Interest Review Committees, the Laboratory and Research Safety Committee, and the Institutional Biosafety Committee. IRB chairs and directors serve on the HRPP Advisory Council. IRB staff representatives serve on these and other committees and provide direction to eResearch initiatives. This

integrative approach facilitates communication of new legal and policy developments throughout the HRPP organization.

III.IRB CHAIRS, MEMBERS, AND STAFF EDUCATION

IRB chairs, members, and staff are trained through a detailed orientation procedure to provide them with the knowledge and skills to effectively discharge their duties and uphold the federal and local laws, University policies, and ethical standards on research with research participants. Continuing education for IRB staff and members is also required and is provided in the form of workshops, presentations, national webinars, and printed and electronic materials that are shared on an on-going basis.

Details of the initial orientation procedure, continuing education requirements, and evaluations of IRB Chairs, members, and staff are described in the IRB SOPs.

IV.RESEARCHERS AND RESEARCH STAFF EDUCATION

A. IRB Educational Activities

The U-M IRBs are committed to providing educational activities that supplement required training for human research protection and are tailored to meet the on-going educational needs of the research community. The activities are designed to improve the understanding of regulatory requirements, IRB application completion, and special topics related to research with research participants. Websites of the U-M IRBMED and IRB-HSBS provide detailed descriptions of the educational offerings as well as access to online materials.

B. MICHR Educational Activities

MICHR supports clinical research at the University through education and study management services. MICHR offers an extensive selection of courses, workshops, and seminars to the U-M research community, designed to meet the needs of students, faculty, and staff. The educational offerings include: pre-doctoral, post-doctoral, and study coordinator programs; mentoring; and general education.

The MICHR website has a full description of the offerings and a calendar of events.

C. Additional Educational Activities

Ongoing educational activities and events are available through colleges, schools, departments and institutes throughout the University. Such activities promote compliance and continually enhance the knowledge of human research protections of the U-M research community. Individual schools and departments maintain a list of educational activities and events on their websites and/or in newsletters.

V. RESEARCH PARTICIPANTS AND THEIR COMMUNITIES: ENGAGEMENT, EDUCATION, AND OUTREACH ACTIVITIES

A. General Research Communications

The U-M HRPP is committed to promoting public awareness and trust in research through outreach efforts designed to enhance the understanding of research by participants, prospective participants, and their communities. The HRPP website presents Information to the Public, including key considerations in protections for research participants, frequently asked questions, and a list of resources and related links. Information about progress in research is regularly

distributed through the U-M news service, including the University Record, Michigan Today, Michigan Radio, Michigan Television (UMTV), and Michigan Medicine News. In addition, continuous campus events showcase research for local, national, and international audiences.

B. Research-Specific Communications

When participant consent is not feasible in the context of research involving imminent life-threatening circumstances, the IRB may approve Emergency Research with Exception from Informed Consent (EFIC) under 21 CFR 50.24. Community Consultation Plans (including, where appropriate, consultation carried out by the IRB) are reviewed and approved in the course of the IRB review of EFIC, and may include consultation with representatives of the communities in which the clinical investigation will be conducted and participants will be drawn.

C. MICHR's Community Engagement Program

Several initiatives have been established by MICHR to foster involvement of community members in human research activities at the U-M.

The Community Engagement Program was established with the specific goal of involving the community's expertise and knowledge in improving the quality of U-M clinical health research and producing outcomes that measurably benefit the health of the local communities. Involving the community in the design and conduct of programs helps ensure that research participants understand intervention content and that research questions are reliable and valid.

The Community Engagement Program focuses on the following specific aims:

- Strengthen community-university partnerships emphasizing power-sharing processes to ensure research priorities directly reflect community and practitioner needs;
- Partner with community members, community-based organizations, and practice networks to stimulate and sustain a robust program of community-based participatory research and implementation/translation science;
- Develop programs and train researchers, practitioners, and community partners in community engagement, community-based participatory research methods, cultural sensitivity, and implementation science; and
- Develop mechanisms that accelerate dissemination and implementation of research results across health care systems practitioners, and communities.

D. UMHealthResearch.org

MICHR has also established the U-M Health Research website to educate the community on research opportunities at the U-M and facilitate participant recruitment in clinical research. Interested study participants may use the tool to search for open research studies at the U-M using various parameters, express interest in studies, communicate securely with study teams, and receive personalized study recommendations. Study teams, in turn, may use the tool to search for eligible study participants.

The U-M Health Research website is also described in a brochure that is distributed in U-M health clinics, in various outreach events, and by community partners.

E. Additional Community Engagement Initiatives

Colleges, schools, departments and other units throughout the University and the Health System have initiatives geared toward increasing and improving community involvement in research with research participants. Individual schools and departments maintain a list of educational activities and events on their websites and/or in newsletters.

F. Evaluation of Community Outreach Programs

While each of the programs listed above have internal processes for evaluating their outreach activities, the HRPP Advisory Council considers the institution's overall outreach periodically.