

**Case Western Reserve University-
Faculty Handbook:
University Standards for Human Research Protection
Revised April 2015**

Purpose

The promotion of scholarship and the discovery of new knowledge through research are among the major functions of Case Western Reserve University (CWRU) as an institution of higher learning. If this research is to be meaningful and beneficial to humanity, involvement of human subjects as study participants is necessary. It is imperative that investigators in all disciplines protect the rights and welfare of human subjects.

University policy and federal regulations mandate compliance with all applicable requirements. Moreover, faculty investigators also have a moral obligation to humankind. The interests of society and the rights of individual subjects must be protected as investigators carry out the mandate to advance knowledge. Research may entail risks to human subjects. Therefore, investigators are obligated to weigh those risks in light of potential benefits to the subject and/or to society.

Mission

The mission of CWRU's Human Research Protection Program (HRPP) is to protect the rights and welfare of human research subjects by ensuring that the oversight of human research is appropriate and in accordance with institutional, federal, state and local requirements, as well as the ethical principles promulgated by The Belmont Report.¹

Scope

The CWRU HRPP covers all human research conducted by any student, employee, trainee, or faculty member (whether paid or unpaid) of CWRU ("CWRU investigator"). It includes any human research conducted at cooperating institutions pursuant to a grant, contract, cooperative agreement, or other award to CWRU. Cooperating institutions include: University Hospitals of Cleveland (UHC), the MetroHealth System (MHS), the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC) and the Cleveland Clinic Foundation (CCF). Reliance agreements in place allow CWRU to defer to the IRBs at these institutions for local protocol review. Hereafter, these institutions shall be referred to as "member institutions" under the CWRU HRPP.

Definitions

Research is defined in 45 CFR 46 as "a systematic investigation designed to develop or contribute to generalizable knowledge." Therefore, any systematic investigation designed to generate results for the purpose of publication (e.g., dissertation, thesis, journal, book, or technical report) or public presentation (e.g. speech, poster, panel, symposium) is considered to be research.

Human subject is defined in 45 CFR 46 as "a living individual about whom an investigator (whether professional or student) conducting research obtains:

¹ Belmont Report (1979). *The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research*. Retrieved February 24, 2015, from hhs.gov/ohrp/humansubjects/guidance/belmont.html

- (1) Data through intervention or interaction with the individual, or
 - (2) Identifiable private information.”
- **Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
 - **Interaction** means communication or interpersonal contact between investigator and subject.
 - **Private Information** means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information an individual can reasonably expect will not be made public (for example, a medical record).
 - **Identifiable Information** means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

Minimal Risk is defined in 45 CFR 46.102(f) as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Responsible or Principal Investigator is the person responsible for the conduct of a human research study at one or more sites, whether on- or off-campus. If the human research study is conducted by a team of individuals, the responsible/principal investigator is the responsible leader of the team. The responsible/principal investigator is accountable for ensuring that the team complies with all rules and regulations and engages with human subjects properly and ethically.

An **Institutional Review Board (IRB)** is a specially constituted review body established or designated by an entity to protect the rights and welfare of human subjects in biomedical or behavioral research [45§46.102(g), .107,.108,.109].

Conditions under Which Investigations Involving Human Subjects May Be Pursued under the CWRU HRPP

1. Ethical Principles and Regulatory Mandates

Human research conducted under the auspices of the CWRU HRPP must be carried out in an ethical manner and in accordance with the principles promulgated by The Belmont Report: respect for persons, beneficence, and justice. In addition, investigators must comply with all applicable federal, state and local requirements related to the protection of human subjects, including Department of Health and Human Services (DHHS) regulations (i.e., 45 CFR 46) and all relevant requirements of other regulatory and funding agencies. CWRU maintains a Federalwide Assurance (FWA) with DHHS. Research must not begin until investigators have received review and approval or verification of exemption by one of the Institutional Review Boards (IRBs) listed on the CWRU FWA.

CWRU applies its ethical standards to all human research regardless of funding. All human research must undergo review by the appropriate designated IRB(s). Activities that do not meet the definition of human research (e.g., most classroom activities, quality improvement activities, non-scholarly program evaluation, and certain health surveillance activities) do not require

review and approval by one of the IRBs within the CWRU HRPP. When CWRU is engaged in human research that is conducted, funded, or otherwise subject to regulations by a federal department or agency, it will apply the regulations of that agency relevant to the protection of human subjects.

2. Informed Consent

An investigator may involve a human subject in research only if the investigator has obtained the informed consent of the subject or the subject's legally authorized representative, unless consent is waived by an IRB per the regulatory provisions. An investigator shall seek such consent only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of undue influence. Unless written documentation is waived by an IRB, the investigator must provide the participant with an informed consent document written in language that is understandable to the subject or his/her representative. The investigator cannot include in the consent process, either orally or in writing, any language through which the subject or his/her representative is made to waive or appear to waive any of the subject's legal rights, or which releases the investigator, the sponsor, the institution, or its agents from liability for negligence.

The basic elements of informed consent, as described in 45 CFR 46, are as follows:

- 1) statement that study involves research, explanation of purposes of research and expected duration of subject's participation, description of procedures to be followed, and identification of any procedures which are experimental;
- 2) description of risks or discomfort to subject;
- 3) description of benefits to subject or to others;
- 4) disclosure of alternative procedures, if appropriate;
- 5) description of the extent to which confidentiality will be maintained;
- 6) for research involving more than minimal risk, explanation as to whether compensation and medical treatments are available if injury occurs;
- 7) explanation of whom to contact if questions arise about the research, the subject's rights or whom to contact if research related injury occurs; and
- 8) statement that participation is voluntary, that refusal to participate involves no penalty or loss of benefits, and that subject may discontinue at any time.

3. Confidentiality of Data

Investigators are responsible for protecting the rights of research subjects by safeguarding the confidentiality of all individual data and all data that could be used to identify subjects. Should any investigator be called upon to reveal research data which would in any way endanger confidentiality, it is his or her obligation to refuse to divulge such information as privileged communication between researcher and subject, unless compelled by law. The investigator should consult with the Office of Research Administration prior to releasing any such information.

The University, funding agencies, and regulatory bodies have the right to audit study data in order to ensure that human subjects are being protected adequately, and that the University is in compliance with approved protocols and its FWA. Those individuals who perform audits are bound by the same rules of confidentiality as the investigator.

4. Investigator Non-compliance

All CWRU investigators working with human subjects have a responsibility to comply with federal regulations and university policy. Human research non-compliance is defined as conducting research involving human subjects in a manner that disregards or violates federal, state or local requirements, or policies established by the applicable IRB. This can include, but is not limited to, failure to obtain IRB approval for research involving human subjects; inadequate or non-existent procedures for informed consent; failure to follow the approved version of the protocol; failure to follow recommendations made by the IRB to safeguard the rights and welfare of subjects; failure to report adverse events or request permission for proposed protocol changes to the IRB; and failure to provide required ongoing progress reports.

Per the applicable regulations, IRBs have the authority to review allegations of human research non-compliance for studies they oversee. An IRB may receive allegations in several different ways, including quality assurance auditing reports, subject complaints, internal allegations, or investigator self-reporting.

The CWRU IRB is required to report serious or continuing non-compliance to federal regulatory entities and to funding agencies or other sponsors. Additionally, CWRU is required to report serious or continuing non-compliance to federal regulatory entities when the research is federally funded and when one of CWRU's affiliated hospital IRBs is the IRB of record.

5. Faculty Advisor Responsibility for Student Research

A faculty member advising student research projects* involving human subjects is responsible for assuring that the rights and welfare of the subjects of student research are adequately protected. CWRU expects that advisors will take an active part in preparing students for the role of researcher, instructing them in the ethical conduct of research and assisting in the preparation of IRB applications. After protocol approval, the advisor should meet regularly with his/her students in order to review their work and progress. While a student serves as the primary researcher for the protocol, the faculty advisor is ultimately responsible for the protection of the student's human subjects. A faculty member's electronic "signature" on the application indicates his/her acceptance of responsibility to comply with all administrative and federal regulations.

* Simulated research activities in a classroom setting for purposes of teaching research techniques typically is not designed to develop or contribute to generalizable knowledge and therefore is not regulated as research.

CWRU IRB Review

All protocols, correspondence, notifications, outcomes, and stipulations pertaining to a social/behavioral/educational research study must be submitted and received via the CWRU IRB electronic system.

Exempt Determination. All research involving human subjects, even if exempt from federal regulation, must be submitted to the appropriate IRB. Research may be exempt from IRB review if it meets the criteria described in 45 CFR 46. Determination of exemption must be made in accordance with the policy of the applicable IRB. If a determination of exemption is made, investigators are still responsible for ethical conduct of human research in accordance with The Belmont Report.

Expedited Review. Expedited review is a procedure through which human research posing no more than minimal risk may be reviewed and approved without convening a meeting of the full IRB. DHHS regulations² specifically define when minimal-risk research can receive expedited review by an IRB.

Full Review. All research that has not received an exemption determination or an expedited review must be reviewed at a convened meeting of the IRB where a quorum of voting members is present.

Amendments. Changes to a study, including, but not limited to, the enrollment criteria or sample size, recruitment methods, consent form language, procedures for data collection, or study interventions require prior approval by the IRB*. Investigators wanting to change a procedure in a study that has already been approved by an IRB must prepare a written description of the proposed change and the reason for the change. Upon review of the proposed amendment, the IRB will then reassess the balance of risks to benefits.

*In the unusual situation where a protocol change is required to avoid an immediate apparent hazard to a subject, the investigator may make the change prior to obtaining IRB approval but must immediately inform the IRB of the occurrence.

Adverse Events. An adverse event is defined as any undesirable and unintended (although not necessarily unexpected) impact on the subject, as a result of a study intervention.³ Investigators must report in writing to the relevant IRB all adverse events in accordance with the IRB's policies and procedures for reporting such events.

Conduct of Biomedical Human Research

The CWRU IRB reviews only social/behavioral/educational and other non-biomedical human research.

When CWRU investigators wish to engage in biomedical human research, including all human research subject to FDA regulations (tests of drugs, devices, and biologics, and other biomedical interventions), they must seek review and approval from the IRB at the affiliated clinical site where the study will take place. The CWRU-affiliated hospital IRBs that have agreements with CWRU to review biomedical research are:

- University Hospitals of Cleveland
- MetroHealth Hospital
- The Cleveland Clinic Foundation
- *The Louis Stokes Cleveland Veterans Affairs Medical Center (LSCVAMC)

² (45§46.110)

³ <http://www.hhs.gov/ohrp/policy/advevntguid.html>

Any questions about whether a research activity is considered biomedical or otherwise subject to FDA regulations should be referred to a representative from the CWRU IRB who will provide assistance.

*Per Central VA policy, the Louis Stokes Cleveland Veterans Affairs Medical Center IRB cannot be the IRB of record for CWRU research. Therefore, unless the CWRU PI has a VA appointment, another CWRU hospital IRB will need to be the IRB of record for CWRU for biomedical research conducted at the LSCVAMC. The CWRU Research Compliance Officer facilitates this process.

International Research

All human research, regardless of funding, performed outside the United States must obtain appropriate institutional IRB approval according to federal regulations and the FWA. Typically, this means IRB approval from CWRU or one of its affiliate IRBs plus local approval at the study site. The university recognizes that the procedures normally followed in the foreign countries may differ from those set forth in U.S. federal regulation.

All applicable ethical standards and regulations are applied consistently to all human research, regardless of whether it is conducted domestically or in another country, including:

- Confirming the qualifications of investigators for conducting the research
- Conducting initial review, continuing review, and review of modifications to previously approved research
- Post-approval monitoring; quality assurance
- Handling of complaints, non-compliance, and unanticipated problems involving risks to subjects or others
- Consent process (when applicable)
- Ensuring all necessary approvals are met
- Coordination and communication with local IRBs

CWRU HRPP Components

Institutional Official

CWRU's Vice President for Research is designated as the Institutional Official (IO) for the CWRU HRPP. In addition to oversight of the HRPP, the Institutional Official ensures that CWRU evaluates Conflicts of Interests in research and that education on the responsible conduct of research is conducted.

The Institutional Official has the authority to take the following actions or delegate these authorities to a designee:

- Allocate resources within the HRPP budget.
- Appoint and remove CWRU IRB members and IRB chairs.
- Approve and rescind authorization agreements for CWRU IRBs.
- Suspend or terminate research approved by the CWRU IRB.
- Disapprove research approved by the CWRU IRB.

Organizational Official

The Associate Vice President for Research is designated as the Organizational Official. The Organizational Official is responsible for oversight of, among other things, policies,

procedures, and business decisions related to how research and sponsored project administration are overseen and monitored.

The Organizational Official has the authority to take the following actions or delegate these authorities to a designee:

- Create the HRPP budget.
- Make personnel decisions.
- Determine upon which IRBs the university will rely⁴.
- Place limitations or conditions on an investigator's or research staff's privileges to conduct human research.
- Develop policies and procedures related to the HRPP that are binding on the university.

The Organizational Official has the responsibility to:

- Oversee the review and conduct of human research under the jurisdiction of the HRPP
- Periodically review this plan to assess whether it is providing the desired results and recommend amendments as needed.
- Establish policies and procedures designed to increase the likelihood that human research will be conducted in accordance with all applicable ethical and legal requirements.
- Institute regular, effective, educational and training programs for all individuals involved with the HRPP.
- Ensure that the research review process is independent and free of undue influence, and ensure that officials of the organization cannot approve research that has not been approved by one of the IRBs designated by the organization.
- Implement a process to receive and act on complaints and allegations regarding the HRPP.
- Implement an auditing program to monitor compliance and improve compliance in identified problem areas.
- Investigate and remediate identified systemic problem areas and, where necessary, remove individuals from involvement in the HRPP.
- Ensure that the HRPP has sufficient resources, including IRBs appropriate for the volume and types of human research to be reviewed, so that reviews are accomplished in a thorough and timely manner.
- Fulfill federally-mandated educational requirements.

CWRU Investigators and Study Staff

Investigators and research staff have the responsibility to:

- Understand the definition of Human Research.
- Consult the relevant IRB when there is uncertainty about whether an activity is human research.
- Not conduct human research or allow human research to be conducted without review and approval by an IRB designated in the CWRU FWA.
- Comply with institutional, federal, state and local requirements, as well as the ethical principles promulgated by The Belmont Report.
- Follow HRPP requirements.

⁴ The organizational official can make a determination about whether CWRU will enter into an inter-institutional agreement to relay on another IRB for review and approval of research.

- Follow IRB policies and procedures.
- Comply with all determinations and additional requirements of the IRB, the IRB chair, and the Organizational Official.
- Report allegations of undue influence regarding the oversight of the HRPP or concerns about the HRPP to the Organizational Official.
- Report allegations or findings of non-compliance with the requirements of the HRPP to the IRB.

Institutional Review Boards (IRB)

The IRBs relied upon by CWRU are listed in CWRU's FWA and on the CWRU IRB Website (<https://research.case.edu/Compliance/>).

Reliance on an IRB not listed in CWRU's FWA requires an Institutional Authorization Agreement for IRB review (IAA) executed by the Institutional or Organizational Official.

The CWRU IRB, as well as any IRBs relied upon by CWRU, has the authority to, for the studies they are monitoring:

- Approve, require modifications to secure approval, and disapprove human research.
- Suspend or terminate approval of human research not being conducted in accordance with an IRB's requirements or that has been associated with unexpected serious harm to subjects.
- Observe, or have a third party observe, the consent process.
- Determine whether an activity is human research.
- Determine whether additional protections are warranted for studies involving vulnerable subject populations.
- Evaluate financial interests of investigators and research staff and have the final authority to decide whether the financial interest and management plan, if any, allow the human research to be approved.
(http://www.case.edu/president/facsen/frames/handbook/conflicts_of_interest.htm)

IRB members and IRB staff have the responsibility to follow HRPP policies and procedures, including disclosure of outside financial interests and recusal from review of protocols with which the member or staff may have a conflict.

Legal Counsel

Legal Counsel has the responsibility to:

- Provide legal advice upon request to the Institutional Official, Organizational Official, IRB, and other individuals involved with the HRPP.
- Help resolve conflicts among applicable laws.

Deans/Department Chairs

Deans and Department Chairs have the responsibility to:

- Assure scientific review and oversee the conduct of human research in their department or school.
- Forward complaints and allegations regarding the HRPP to the Organizational Official.
- Affirm that each human research study proposed to be conducted in their department or school can be done responsibly by the study team using the resources described in the proposal.

Office of Research Administration

The Office of Research Administration (and similar offices with delegated authority, such as the School of Medicine Office of Grants and Contracts) has the responsibility to review contracts and funding agreements for compliance with HRPP policies and procedures.

Education and Training

IRB members, IRB staff, and others involved in the review of human research must complete initial and continuing training on the protection of human subjects.

Investigators and research staff must complete the initial and continuing training on the protection of human subjects.

Reporting and Management of Concerns

Questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the HRPP may be reported orally or in writing. Employees are permitted to report concerns on an anonymous basis. Concerns may be reported to the IRB Office, the IRB Chair, the Organizational Official, Office of General Counsel, Integrity Hotline, Internal Audit Department, Deans, or Department Chairs.

The relevant IRB has the responsibility to investigate allegations and findings of non-compliance related to conduct of research for studies under its jurisdiction and take corrective actions as needed. The Organizational Official has the responsibility to investigate all other reports and take corrective actions as needed. In some instances, the IRB and the Organizational Official may, for different purposes, both be required to investigate the same matter, or may collaborate or share resources as necessary.

Employees who report in good faith possible compliance issues shall not be subjected to retaliation or harassment as a result of the reporting. Concerns about possible retaliation should be immediately reported to the Organizational Official or designee.

To make such reports, contact:

The Office of the Associate Vice President for Research
Sears Library Building, 6th Floor.
2083 Martin Luther King, Jr. Drive
Cleveland, Ohio 44106-7230
216-368-0143

Monitoring and Auditing

In order to monitor and assure compliance, auditors who have expertise in federal and state statutes, regulations and organizational requirements will conduct periodic not-for-cause audits.

Disciplinary Actions

The IRB and the Institutional Official may terminate or suspend IRB approval. In addition, the IRB and/or the Institutional Official and/or Organizational Official may place limitations or conditions on an investigator's or research staff's privilege to conduct human research whenever, in the opinion of the IRB and/or the Institutional Official and/or Organizational Official, such actions are required to maintain the integrity of the HRPP.