

B. University Policy on Human Research Protection*

The promotion of scholarship and the discovery of new knowledge through research are among the major functions of Case Western Reserve University as an institution of higher learning. If this research is to be meaningful and beneficial to humanity, involvement of human subjects as experimental participants is necessary. It is imperative that investigators in all disciplines strive to protect human subjects. University policy and federal regulations demand compliance. Moreover, faculty investigators also have a moral obligation to humankind. The rights of society and the rights of individual subjects must be protected at the same time that investigators are privileged to 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.

The Case Human Research Protection Program (Case HRPP) covers all human research conducted by any student, employee, faculty member of Case Western Reserve University (Case), University Hospitals of Cleveland (UHC) and The MetroHealth System (MHS) as part of his or her job responsibilities with that organization, or any human research conducted by an independent contractor of these organizations as part of the organization's contract. In addition, for any human research in which Case acts as the grantee, employees of the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC) and the Cleveland Clinic Foundation (CCF) are also responsible for complying with the Case HRPP. Hereafter, these institutions shall be referred to as "member Institutions" under the Case HRPP. The following policy statements enunciate the guidelines under which investigations involving human subjects may be pursued through the Case HRPP:

1. Ethical Principles and Regulatory Mandates

Human subject research associated with the Case HRPP must be carried out in an ethical manner and in accordance with The Belmont Report. In addition, investigators must comply with all applicable federal, state and local regulations that related to the protection of human subjects, including any and all Food and Drug Administration regulations (i.e., 21 CFR 50 and 56) and any and all Department of Health and Human Services (DHHS) regulations (i.e., 45 CFR 46). Case maintains a Federalwide Assurance (FWA) with DHHS and applies the requirements of this assurance to all research regardless of funding. Research must not begin until investigators have received review and approval to conduct such research by one of the Institutional Review Boards (IRBs) listed on the Case FWA.

The IRB Advisory Committee (IAC) was created to ensure that oversight of human subject research is appropriate and in accordance with institutional, federal and state regulations and local mandates. It is empowered by this policy to create procedures and programs for the Case HRPP to accomplish this mission. The Provost will act as the Institutional Official for the Case HRPP.

2. Definitions

"Research" is defined in 45 CFR 46 as "systematic investigation designed to develop or contribute to generalizable knowledge." Therefore, any investigation designed to generate results that could be published (e.g. journal, book, or technical report) or presented at a conference is considered to be research. Research conducted with human subjects for masters or doctoral theses also must receive IRB approval prior to initiation.

"Human subject" is defined in 45 CFR 46 as a "living individual about whom an investigator (whether professional or student) conducting research obtains: data through intervention or interaction with the individual or identifiable private information." See 45 CFR 46 for definitions of "intervention," "interaction," and "private information." Subjects may include, for example, persons involved in behavioral science studies; normal volunteers; donors of services; in-patients and out-patients; living donors of body fluids, organs, and tissues; and members of the general population who may be involved in environmental or epidemiological studies or similar activities.

"Minimal Risk" is defined in federal regulations at 45 CFR 46.102(f) and 21 CFR 56.102(i) 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.

3. 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. 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 coercion or undue influence. The investigator must provide the information in written documentation, which uses language that is understandable to the subject or representative. The investigator cannot include in the consent process, either orally or in writing, any language through which the subject or 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. Informed consent is a process.

The basic elements of informed consent 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.
4. Privacy and Confidentiality of Data

University investigators are responsible for protecting the right to privacy of research subjects by safeguarding the confidentiality of all individual data and all data that could in any way be attributed to or used to identify the individuals. Should any investigator be called upon by any individuals or groups, private or public, 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.

However, the University itself has the right to audit data in order to ensure that human subjects are being adequately protected and that the University is in compliance with the FWA. Those individuals performing the audit are bound by the same rules of confidentiality as the investigator.

5. Investigator Non-compliance

All investigators working with human subjects have a responsibility to comply with federal regulations and University policy. Human subject non-compliance is defined as conducting research involving human subjects in a manner that disregards or violates federal regulations governing such research 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; inadequate supervision in research involving experimental drugs, devices or procedures; failure to follow the approved version of the protocol; failure to follow recommendations made by the IRB to insure the safety of subjects; failure to report adverse events or proposed protocol changes to the IRB; and continued failure to provide ongoing progress reports.

Per the applicable regulations, IRBs have the authority to review allegations of human subject non-compliance for their particular institution. An IRB may receive allegations in several different ways including, quality assurance auditing reports, subject complaints, internal allegations, or investigator self-reporting. The process by which an IRB reviews allegations should be determined by the seriousness of the allegations and the probability or occurrence of subject harm. It is important to note that harm to subjects is not limited to physical harm, but also includes social/psychological harms such as breach of confidentiality.

6. Scope of IRBs under the FWA

Human subject research under the scope of the Case HRPP must be reviewed by one or more federally-registered IRBs at Case, UHC, MHS, and CCF. Additional federally-registered IRBs outside of the Case HRPP may also be designated under the appropriate FWA to review collaborative human research on an as needed basis. An IRB has the regulatory authority to take any action necessary to protect the rights and welfare of human subjects under the Case HRPP including:

To approve, required modifications to secure approval, disapprove, all research activities overseen and conducted by the organization;

To suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected harm to participants;

To observe, or have a third party observe, the consent process and the conduct of research.

7. Types of Review

Exempt Review. All research involving human subjects must be submitted to the appropriate IRB. Determination of exemption must be made by an appropriate IRB. Research may be exempt from IRB review if it meets the criteria described in 45 CFR 46. FDA regulations do not allow for exemptions for research (except in the case of emergency use of test article), therefore research subject to such regulation cannot be exempt. If a determination of exemption is made, investigators are still responsible for ethical conduct of research with human subjects in accordance with The Belmont Report.

Expedited Review. Expedited review is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the full IRB. DHHS and FDA regulations specifically define when minimal-risk research can receive expedited review by an IRB.

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

Amendments. Investigators wanting to change a procedure in a study that has already been approved must prepare a written description of the change and the reason for the change. Such changes include the entry or enrollment criteria of subjects, procedures for data collection, or some activity or procedure that must be changed due to an adverse event. The IRB will then reassess the balance of risks to benefits. In light of the reassessment, the IRB may require the research to be modified or terminated. Any amendment to a study must be reviewed and approved in accordance with IRB policies prior to initiation of the change.

Adverse Events. An adverse event is defined as any undesirable and unintended (although not necessarily unexpected) impact on the subject, as a result of therapy or other intervention. Investigators must report in writing to the IRB all adverse events in accordance with the IRB's policies and procedures for reporting such events. If during the course of an investigator's approved research subjects experience adverse effects or new knowledge impacts research design, investigators must inform subjects of any information deemed important by the IRB, which may affect a subject's willingness to continue participation.

8. Faculty Advisors are Responsible for Student Research

A faculty member assigning research projects involving human subjects must take an active role in assuring that the subjects of student research are adequately protected. The University 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 the student 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 human subjects. A faculty member's signature on the application indicates their willingness to comply with all administrative and federal regulations.

9. International Research

All human subject research, regardless of funding, performed outside the United States must obtain appropriate institutional IRB approval according to federal regulations and the FWA. The University recognizes that "the procedures normally followed in the foreign countries may differ from those set forth in this policy." The research, however, may be approved if "the procedures prescribed by the (foreign) institution afford protections that are at least equivalent to those provided in the FWA."