

Clarification of Human Subjects Research Definitions, Upcoming Changes in Research Processes

Introduction

Clinical research (a type of Human Subjects Research activity) is a complex undertaking in which policies and procedures emerge and change frequently. Clinical research may involve many organizations outside of NIH, such as the pharmaceutical industry, not-for-profit organizations, the Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), Department of Health and Human Services (DHHS) and Center for Medicare and Medicaid Services (CMS). DHHS regulations (45 CFR 46) apply to research funded in whole or part by DHHS. FDA regulations (21CFR 50 and 21 CFR 56) apply to research involving products regulated by FDA. Some clinical research funded by NIH may be subject to both sets of regulations.

Contract and Grant Administration (CGA), the Office of Regulatory Affairs (ORA), and the Clinical and Translational Sciences Institute (CTSI) have collaborated on clearly defining the basic types of human research activity occurring at MSU. This collaboration was based upon the (DHHS) and the Food and Drug Administration (FDA) definitions of Human Subject Research and Clinical Investigations involving Human Subjects, the DHHS and FDA definitions of clinical trials, the National Institutes of Health (NIH) definition of clinical research, and Office of Human Research Protections (OHRP) language on the topic.

For the MSU Human Research Protection Program's (HRPP) various Institutional Review Boards (IRBs) and for the CTSI, these definitions help to characterize and prompt the type of IRB review and other types of regulatory oversight that will be required (human subject protection, federal registration, financial oversight and compliance). At CGA, these distinctions help to segregate human research projects with respect to application of the appropriate indirect cost rate (IDC), administration of the contract and account, and facilitate collection of metrics on the different types of human research our institution is contracting to perform.

Currently, clinical trials (a form of clinical research as defined by NIH and FDA) are not clearly defined at MSU. Due to the additional regulations and oversight required for this type of research, clinical trials will now be separated from the general category of clinical research, and will have further delineation in cases where the MSU colleague is a primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the trial (investigator-initiated clinical trials). Please refer to the CGA Project Classification Decision Diagram.

Changes to Human Subject Research Processes:

The changes in classification for Human Subject Research activity will occur both through CGA via transmittal language (Project Nature Section, MSU-IP indication), and through the IRB application language (Question # 16- Research Category). Human research classifications, which will be the same across the institutional offices, will be based upon these new definitions (see Definitions at the end of this section for clarification), and will require the following upcoming changes through CGA and IRB:

CGA

1. Upcoming changes to 'Project Nature' section of CGA transmittal:

- The 'Project Nature' section will have the following categories of Human Research from which to select: Research- Non-Clinical with Human Subjects, MSU investigator-initiated; Non-Clinical with Human Subjects, Agency-initiated, Research- Clinical with Human Subjects, MSU investigator-initiated; Research- Clinical with Human Subjects, Agency-initiated; Research-Clinical Trial with Human Subjects, MSU investigator-initiated; Research- Clinical Trial with Human Subjects, Agency-initiated.

2. Determination of corresponding indirect cost rate (IDC) on CGA transmittal:

- Is an MSU colleague a primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the project? If so, the project is investigator-initiated, so check the applicable IDC rate below.

Investigator-initiated?		IDC Rate
Yes:	On-campus	52%*
	Off-campus ⁺	26%*
No:	Industry- clinical trials, research, and testing	26%*
	Federal or other- On-campus	52%*
	Federal or other- Off-campus ⁺	26%*
	State of Michigan	Call CGA (517-355-5040)
⁺ Off-campus: ≥ 50% of project expenses are at an off-campus location		
* Unless another rate is documented as general policy from a not-for-profit sponsor and accepted by MSU, or waiver is submitted to and approved by VPRGS.		

IRB

Changes to Initial Application

- Question # 16 now includes the new classification system for human research with the options of Clinical Research and Clinical Trial, with an additional subsection for indication of trial phase for those projects falling under clinical trial classification; trials that are ‘investigator-initiated’ will also need to be indicated as such in this section.

The New Human Subject Research Classification System:

1. Research -Non-Clinical with Human Subjects, MSU Investigator-Initiated

- Typified by human subject research fitting DHHS or FDA definitions [*link to CTSI definition page*], but not classified as clinical research or clinical trial research. Examples: agriculture (food testing research); educational research; some in-vitro studies utilizing human tissues that cannot be linked to living individuals; some fisheries and wildlife survey projects; some social science research.
- MSU investigator-initiated is defined as an MSU colleague being a primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research.

2. Research -Non-Clinical with Human Subjects, Agency-Initiated

- Typified by human subject research fitting DHHS or FDA definitions [*link to CTSI definition page*], but not classified as clinical research or clinical trial research. Examples: agriculture (food testing research); educational research; some in-vitro studies utilizing human tissues that cannot be linked to living individuals; some fisheries and wildlife survey projects; some social science research.
- Agency-initiated is defined as an agency (ie- industry, federal, state, foundation, etc) being the primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research.

MSU is paid for providing services (data, samples, etc) as required by the sponsor-generated protocol, but has no direct input on or influence over the research design or protocol.

3. Research- Clinical with Human Subjects, MSU Investigator-Initiated

- Defined by NIH as patient-oriented research; research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Also includes epidemiologic and behavioral studies as well as outcomes research and health services research. Examples: retrospective studies, registries, research that involves collection and research on human specimens or information but that does not involve an intervention.
- Typified by funded, contract or grant-driven research (sponsored by NIH, company, foundation, etc.), or internally funded pilot studies on the path to grant writing. Some clinical research projects may not be externally funded.
- Clinical research that is not specifically defined as a clinical trial, and that is MSU-investigator-initiated. MSU investigator-initiated is defined as a clinical trial wherein the MSU colleague is a primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research. Although clinical trials are a subset of clinical research, they will have a separate classification on the transmittal.

4. Research- Clinical with Human Subjects, Agency-Initiated

- Defined by NIH as patient-oriented research; research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Also includes epidemiologic and behavioral studies as well as outcomes research and health services research. Examples: retrospective studies, registries, research that involves collection and research on human specimens or information but that does not involve an intervention.
- Typified by funded, contract or grant-driven research (sponsored by NIH, company, foundation, etc.), or internally funded pilot studies on the path to grant writing. Some clinical research projects may not be externally funded.
- Clinical research that is not specifically defined as a clinical trial, and that is agency-initiated. Agency-initiated is defined as an agency (ie- industry, federal, state, foundation, etc) being the primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research. MSU is paid for providing services (data, samples, etc) as required by the sponsor-generated protocol, but has no direct input on or influence over the research design or protocol. Although clinical trials are a subset of clinical research, they will have a separate classification on the transmittal.

5. Research- Clinical Trial with Human Subjects, MSU Investigator-Initiated

- Typified by prospective biomedical or behavioral research studies of human subjects that are designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Examples: drug and device trials, some behavioral intervention studies and outcomes research studies. Study design follows phase definitions (which may not necessarily be indicated in project title).
- MSU investigator-initiated is defined as a clinical trial wherein the MSU colleague is a primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research.

6. Research- Clinical Trial with Human Subjects, Agency-Initiated

- Typified by prospective biomedical or behavioral research studies of human subjects that are designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Examples: drug and device trials, some behavioral intervention studies and outcomes research studies. Study design follows phase definitions (which may not necessarily be indicated in project title).

- Agency-initiated is defined as an agency (ie- industry, federal, state, foundation, etc) being the primary or contributing designer of the research endeavor and/or writer of the protocol/scope of work for the research. MSU is paid for providing services (data, samples, etc) as required by the sponsor-generated protocol, but has no direct input on or influence over the research design or protocol.

Definitions

Research- DHHS Definition (45 CFR 46.102(d))

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Systematic investigation:

- Attempts to answer research questions (in some research, this would be a hypothesis).
- Is methodologically driven, that is, it collects data or information in an organized and consistent way.
- The data or information is analyzed in some way, be it quantitative or qualitative data.
- Conclusions are drawn from the results.

Generalizable knowledge is knowledge that is “expressed in theories, principles, and statements of relationships” that can be widely applied to our experiences. Generalizable knowledge is usually created to share with other people, such as through presentations and publications. Masters’ theses and Ph.D. dissertations are considered to present generalizable knowledge.

“Generalizable knowledge” would include one or more of the following concepts:

- The knowledge contributes to a theoretical framework of an established body of knowledge.
- The primary beneficiaries of the research are other researchers, scholars and practitioners in the field of study.
- Publication, presentation or other distribution of the results is intended to inform the field of study.
- The results are expected to be generalized to a larger population beyond the site of data collection.
- The results are intended to be replicated in other settings.
- Web based publication for professional purposes

Human Subject Research- DHHS Definition (45 CFR 46.102 (d,f))

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

- (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 includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Clinical Investigation- FDA definition (21 CFR 50, 56, 312, 812)

Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic act (21 U.S.C 321-392), or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58, regarding non-clinical laboratory studies. 21 CFR 50.3(c).

For an activity involving drugs: “Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, and experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.” 21 CFR 312.3(b).

For an activity involving devices: “Investigation” means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.” 21 CFR 812.3(h).

Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

For clinical investigations or research involving devices, the definition of “subject” includes the use of specimens, even if the specimen is unidentified. While such research is not considered “human subjects” under the DHHS regulations, such research would be considered “subjects” under the FDA regulation for certain types of research. MSU OHRP manual, section 4-3.

Clinical Research- NIH Definition:

1. Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:

- Mechanisms of human disease
- Therapeutic interventions

- Clinical trials
 - Development of new technologies
2. Epidemiologic and behavioral studies.
 3. Outcomes research and health services research.

Clinical Trial- NIH/FDA Definition:

A prospective biomedical or behavioral research study of human volunteers that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. There are different kinds of clinical trials, including those to study:

- prevention options
- new treatments or new ways to use existing treatments
- new screening and diagnostic techniques
- options for improving the quality of life for people who have serious medical conditions

Clinical trials are conducted according to a plan called a protocol. The protocol describes what types of patients/volunteers may enter the study, schedules of tests and procedures, drugs/dosages (if applicable), and length of study, as well as the outcomes that will be measured. Each person participating in the study must agree to the rules set out by the protocol.

Clinical trials of an experimental drug, treatment, device, or intervention may proceed through four potential phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

NIH-Defined Phase III Clinical Trial. An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Quality Assurance/Quality Improvement (suggested guidelines)

- Excerpted from Penn St. University’s Human Subjects Protection Office
- For reference in determination of research vs QA/QI

	Research	QI/QA
Purpose	Test a formal hypothesis	Assess a process, program or system
Starting Point	A prospectively designed, formal, written research hypothesis	An established set of standards
Benefits	Knowledge sought may not benefit subjects involved in study	Knowledge sought directly benefits process/program/system
Risks/Burdens	May put subjects at risk	No risk, with exception of possible loss of privacy/confidentiality
Data Collection	Systematic data collection	Systematic data collection
End Point	Answer research question	Improve the program/process/system
Testing/Analysis	Determine validity of hypothesis	Compare the program/process/system to established set of standards
Intended Result	Share findings with individuals associated with the investigation and individuals not associated with the investigation	Share findings with only those individuals associated with the process/program/system.