

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &
IMPLEMENTATION**

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

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SOP 20 - NIH HRPP REQUIREMENTS FOR COLLABORATIVE RESEARCH

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SOP 20 - NIH HRPP REQUIREMENTS FOR COLLABORATIVE RESEARCH

20.1 PURPOSE

This SOP describes NIH policies and points to consider when NIH employees participate in research collaborations that involve human subjects. These collaborations may involve non-NIH sites or individuals who are not NIH employees. This SOP addresses only those collaborations involving human subjects research that require IRB review of the NIH investigator's contributions, otherwise termed "non-exempt" human subjects research under 45 CFR 46.¹

20.2 POLICY

NIH complies with 45 CFR 46 and FDA regulations when NIH employees collaborate in research activities with individuals who are not NIH employees. This SOP and SOPs 20A – Obtaining a Reliance (Authorization Agreement at NIH, 20B – NIH IRB Responsibilities When Reviewing Local Context Considerations for Offsite Research, 20C – Responsibilities When the NIH Intramural Research Program Serves as a Coordinating Center for a Multi-site Trial or Serves as the IRB of Record for a Non-NIH Coordinating Center and 20D – NIH FWA Coverage for Non-NIH Employees Working on NIH Protocols set forth additional NIH requirements for research collaborations.²

20.3 DEFINITIONS

A. Authorization Agreement (also known as a "**Reliance Agreement**"): An agreement between NIH and one or more institutions involved in the same cooperative research (see definition, below) that assigns regulatory responsibilities to a specific IRB. The terms "authorization agreement" and "reliance agreement" are used interchangeably in this SOP. At NIH the

¹ This SOP, however, gives examples of research with de-identified specimens and data to distinguish those research activities from activities that require IRB approval.

² Collaborative research activities may trigger other NIH policy requirements or agreements, such as Authorization (Reliance) Agreements, Memoranda of Understanding (MOUs), Cooperative Research and Development Agreements (CRADAs) and Material Transfer Agreements (MTAs). Reliance Agreements are managed by OHSRP in cooperation with the IRBs. MOUs, CRADAs, and MTAs are managed by other NIH offices.

preferred term is “reliance agreement.” The following terms and phrases are frequently used in the context of authorization/reliance agreements:

1. **Central IRB:** The IRB responsible for reviewing a research protocol for multiple performance sites engaged in the same project. The Central IRB assumes responsibility as the IRB of Record for the performance sites relying on the Central IRB for review of the research project. (See also definition of Centralized IRB Review Process, below.) This “Central IRB” may also be called the IRB of record.
2. **Centralized IRB Review Process:** A centralized IRB review process involves an agreement in which institutions engaged in multi-site cooperative research rely in whole or in part on the review of a single IRB that may or may not be affiliated with the research site(s).
3. **Single Study Agreement:** An authorization/reliance agreement that pertains to only one protocol.
4. **Joint IRB Review Agreement:** An agreement in which two or more institutions divide specified responsibilities for IRB review so that each IRB is responsible for only part of the IRB review and oversight. For example, a Joint IRB Review Agreement might be desirable if investigators at one institution design the protocol and receive identifiable data, but the protocol is implemented at a different institution where the subjects are located. One IRB may approve the protocol but another IRB may approve the consent to ensure that it adequately addresses local concerns. Different research interventions may occur at more than one institution, and each institution may wish to have IRB review and oversight of protocol activities that occur at its own institution. If each site’s IRB is reviewing only a portion of the same protocol, then a reliance agreement is needed to clarify that each institution is relying on the other site’s IRB review and oversight of those specific protocol activities.
5. **Program-Wide Agreement:** This term refers to an authorization/reliance agreement that applies to all future collaborative studies, as defined in the agreement, and conducted by the signatory institutions, unless exceptions are made.

B. Collaboration: Research involving at least one NIH staff person, and individual(s) outside of the staff person's laboratory who may or may not be NIH staff, e.g., individuals from another IC component, a different NIH Institute/Center, or outside of NIH altogether. Collaboration exists if the NIH intramural researcher expects or receives "something in return" as a result of having participated in a research activity. "Something in return" could include data, authorship on a publication, samples or even patent rights. The NIH views authorship as prima facie evidence of collaboration. Collaborative activities may include but are not limited to: the collection of specimens/data from human subjects, visits to institutions to perform research activities, exchange of information containing personal identifiers, preliminary data-collection activities involving human subjects, performance of laboratory testing on or analysis of specimens/data for research purposes; and participation in the creation of a presentation/ manuscript based on research findings and substantive intellectual contributions to research techniques, protocol design, or interpretation of data. Even remote participation -- such as supplying important reagents, performing tests, or analyzing data -- may constitute collaboration if substantive intellectual input exists. However, collaboration does not include mere provision of research tools such as biological materials, cell lines, antibodies, probes, tissue or data, even if the tools are unique, without intellectual contribution to the research in which the tools will be used. Collaboration may involve activities that are not human subjects research, as defined by 45 CFR 46. OHSRP can provide guidance if there are questions in this regard.

C. Cooperative Research: Research in which more than one institution is engaged in human subjects research. 45 CFR 46.114 states: "Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy."

D. Cooperative Research and Development Agreement (CRADA): An agreement authorized by 15 U.S.C. 3710a and approved by the NIH CRADA Subcommittee to make government facilities, intellectual property, and/or expertise available for collaborative interactions with other Federal agencies; units of State or local government; industrial organizations (including corporations, partnerships, and limited partnerships, and industrial development organizations); public and private foundations; nonprofit organizations (including universities); or other persons (including licensees of inventions owned by the Federal agency to

further the development of scientific and technological knowledge into useful, marketable products. CRADAs are authorized only with collaborators who will make significant intellectual contributions to the research project undertaken or will contribute essential research materials or technical resources not otherwise reasonably available to NIH. CRADAs cannot attempt to direct or restrict research in a NIH laboratory. Sponsored research, such as routine, conventional testing, with no collaborative, intellectual contribution, is not appropriate for a CRADA.

E. Coordinating Center (Entity) for Multi-site Studies: A coordinating center is the entity that is responsible for overall planning, document collection, monitoring and communication among all sites participating in a multi-site research project. A Coordinating Center may also be responsible for data management and analysis and may be designated either by a sponsor or by mutual agreement of the participating sites. The sponsor may delegate some of its responsibilities to the coordinating center as discussed in SOP 20C – Responsibilities **When the NIH Intramural Research Program Serves as a Coordinating Center for a Multi-Site Trial or Serves as the IRB of Record for a Non-NIH Coordinating Center.**

F. Dual or Multiple IRB Review: This phrase is used when each institution engaged in **human subjects** research has its own IRB independently review and oversee all aspects of a particular research protocol as conducted at its own institution.

G. Employee: An individual who is engaged in the performance of a Federal function under authority of law or an Executive act and subject to the supervision of an individual named by paragraph (1) in 5 U.S.C. **2105** while engaged in the performance of the duties of his position. **This includes Special Government Employees or Intergovernmental Personnel Act appointees for the purpose of this SOP.**

H. Executive Committee (for a Coordinating Center): A group of individual leaders associated with the study that directs the study and ensures implementation and coordination of strategic plans for the research. The committee participants vary based on the needs of the study. In the case of multi-site studies, this Committee may be comprised of the Lead PI overseeing the implementation of the protocol, the PI of the Coordinating Center and the director of the Steering Committee.

I. Exempt Research: This term refers to a specific list of human subjects research activities that are set forth in 45 CFR 46.101(b). At the NIH, only OHSRP makes determinations about whether a particular research activity is “exempt”. See SOP

6 – Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP)

J. **Federalwide Assurance (FWA):** A Federalwide Assurance is a written commitment by an institution to comply with the **Protection of Human Subjects regulations at 45 CFR 46**. The FWA is filed with the DHHS Office for Human Research Protections (OHRP).

K. **Human Subject:** Under 45 CFR 46.102(f) a human subject is a living individual about whom an investigator (whether professional or student) conducting research obtains:

- a. Data through intervention or interaction with the individual, or
- b. Identifiable private information

L. **Human Subjects Research:** In this SOP, this term refers to activities which: (1) meet the 45 CFR 46 definition of research (45 CFR 46 102(d)); (2) involve human subjects, according to the 45 CFR 46 102(f), and (3) are not exempt from the provisions of 45 CFR 46 under 45 CFR 46.101(b). The term “Human Subjects Research” in this SOP, therefore, always means non-exempt Human Subjects Research. (However, in 45 CFR 46, “human subjects research” includes also research that is exempt from the requirements of 45 CFR 46.)

M. **Intervention:** includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

N. **Interaction:** includes communication or interpersonal contact between investigator and subject.

O. **Individual Investigator Agreement (IIA):** An agreement between an outside collaborator and NIH that extends the NIH FWA to either an individual investigator or institutional investigators who are not covered by an FWA (e.g. physicians in private practice or individuals who work at an institution that does not have an FWA).

- P. **IRB of Record:** The IRB responsible for review of research and determining that the research meets IRB regulatory requirements for approval.
- Q. **Lead IRB:** The IRB responsible for reviewing a research protocol for multiple performance sites engaged in the same project. The lead IRB assumes responsibility as the IRB of Record for the performance sites relying on the lead IRB for review of the research project. (See also definition of Centralized IRB Review Process, above.)
- R. **Local Context:** In this SOP, this term refers to unique legal requirements, cultural or religious values or other site-specific variables that exist at a site where subjects are enrolled in research protocols. NIH expects IRBs to evaluate “local context” when approving and overseeing a research protocol because matters such as consent, privacy and confidentiality may necessitate specific requirements by the IRB before research can begin.
- S. **Material Transfer Agreement (MTA):** An agreement between NIH and another entity, generally utilized when any proprietary material is exchanged and when the receiving party intends to use the material for his/her own research purposes. Neither rights in intellectual property nor rights for commercial purposes may be granted under this type of agreement. MTAs define the terms and conditions under which the recipients of materials provided by either the NIH scientist or the other party may use the materials.
- T. **Memorandum of Understanding:** A written agreement between two or more entities (such as research institutions, government agencies) that outlines the terms and details of an agreement between the parties, including each party’s expected activities and goals.
- U. **Not Human Subjects Research (NHSR):** This term refers to research activities that do not fall within the 45 CFR 46 definition of human subjects research. (See definition of Human Subjects Research, above, which references the regulatory standard.)
- V. **Office for Human Research Protections (OHRP):** OHRP is part of the Office of the Assistant Secretary for Health (OASH) in the Office of the Secretary (OS), U.S. Department of Health and Human Services. This Office provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in all research conducted or supported by the U.S. Department of Health and Human Services (HHS).

W. **Office of Human Subjects Research Protections (OHSRP):** OHSRP is the NIH office that sets policy and provides regulatory oversight for the NIH Human Research Protection Program. This Program promotes the rights and welfare of human subjects who participate in research conducted by the Intramural Research Program of the NIH.

X. **Performance Site (Enrollment Site):** A performance site, or an enrollment site, is a place where human subjects participate in research activities (e.g. often a clinic or hospital). The performance site's location may be different from the location where the IRB review occurs. Subjects are usually enrolled or followed at performance sites.

Y. **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 (45 CFR 46.102 (f)).

Z. **Reliance Agreement:** See definition of Authorization Agreement, above.

AA. **Research:** Under 45 CFR 46.102(d), research is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for the 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. (See SOP 6 – **Processes for** Determinations Made by the Office of Human Subjects Research Protections (OHSRP) Under 45 CFR 46).

BB. **Site Terminology:**

1. **NIH Performance Sites (Enrollment Sites):** Performance sites that are owned or controlled by the NIH, such as the Warren Grant Magnuson Clinical Center on the NIH Bethesda campus. Examples of other NIH-owned or controlled sites include the NIEHS Clinical Research Unit at Research Triangle Park, North Carolina; NIAID Rocky Mountain Laboratories in

Hamilton, Montana; and the NIDDK Phoenix Epidemiology and Clinical Research Branch in Phoenix, Arizona.

2. **Multi-Site Protocol (Multi-Site Research):** Multi-site research/protocols refer to projects that will be conducted at more than one Performance Site. Usually a multi-site study involves conduct of an entire protocol carried out at more than one medical institution or site. Sites may also include schools, nursing homes, community rehabilitation facilities, private practices, individual homes, etc. As part of the protocol application, the investigator shall disclose the entity that will serve as the coordinating center for the project.

CC. Special Volunteer: A “special volunteer” is an individual who meets NIH requirements set forth in NIH Manual Chapter “2300-308-1 – Guest Researcher/Special Volunteer Programs” and has been designated as a Special Volunteer by the NIH. Special Volunteers (SV) are non-NIH Employees who provide research services, direct patient care, clerical support, technical assistance, or any other necessary services for NIH using NIH facilities.

DD. Support: In this SOP, the word “support” means that an institution is assisting with a research protocol at another institution. Support includes, but is not limited to funding and collaboration.

20.4 TWO QUESTIONS THAT SHOULD BE ASKED BEFORE INITIATING COLLABORATIVE RESEARCH

Human subjects research that is conducted or supported by the NIH must comply with 45 CFR 46. When participating in research collaborations, the NIH investigator must determine what entities are engaged in human subjects research and whether the NIH is supporting human subjects research at another institution. This section sets forth issues related to these important questions:

- A. Is the NIH researcher or the collaborating researcher **engaged** in human subjects research?
 1. In evaluating this question, a researcher should apply the regulatory definition of human subject (See 20.3 Definitions) to the particular research activity, and review OHRP guidance, which explains what activities constitute “engagement in human subjects research”. (See

Appendix 1, OHRP Guidance on Engagement of Institutions in Human Subjects Research also available at the following link: <http://www.hhs.gov/ohrp/policy/engage08.html>). OHSRP will assist NIH researchers in evaluating this question.

2. When the NIH researcher *or* the non-NIH collaborator is engaged in human subjects research, that research must be approved by an IRB, either at the NIH and/or by an outside IRB. If the protocol is approved only at an outside IRB, there must be a reliance agreement for NIH to rely on the outside IRB. (See SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH). In other collaborations, when an NIH researcher is not performing “human subjects research” as defined by federal regulations, or when the research is “exempt” from 45 CFR 46, including the requirement for IRB review, under federal regulations, OHSRP must determine that the research can proceed. (See **SOP 5 – Required Review for NIH Research Activities with Human Subjects and Specimens/Data** and **SOP 6 – Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP) Under 45 CFR 46.**)

B. Is the NIH **supporting** human subjects research at another institution?

1. If the non-NIH collaborating researcher is engaged in human subjects research activities, the NIH must ask whether the collaborating institution has a Federalwide Assurance (FWA) and IRB review and oversight. This requirement stems from federal regulations at 45 C.F.R. 46.101 (a) which state: “Except as provided in paragraph (b) of this section, **this policy applies to all research involving human subjects conducted, supported** or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research.” (emphasis added) (Note: paragraph b of the federal regulations is a list of research activities, referred to as “exempt research,” which is considered human subjects research but not subject to the requirements of 45 C.F.R. 46.)
2. Within the United States, most research institutions have FWAs because they obtain funding from DHHS, usually through NIH grants. Many research institutions in other countries do not have FWAs and instead follow the legal requirements of the particular country. If, however, the NIH is **supporting human subjects research** at a foreign institution, the

foreign institution must follow 45 CFR 46. This requires an FWA and IRB approval pursuant to those regulations.

3. In some cases, it is clear that the NIH is providing **support** to human subjects research at another institution. Support may include funding, sending personnel to the site to engage in human subjects research, or providing NIH personnel to analyze identifiable data from the research protocol. In other cases, however, the facts are less clear. For example, an NIH researcher may be analyzing de-identified data obtained from a protocol at another institution. In determining whether NIH is **supporting** human subjects research at that institution, there must be an evaluation of whether results from the NIH will be used to make decisions that impact the human subjects research participation at the other institution. OHSRP can assist with this assessment.

20.5 TYPES OF COMMON RESEARCH COLLABORATIONS

20.5.1 RESEARCH CONDUCTED BY AN NIH RESEARCHER THAT INVOLVES ONLY THE USE OF SPECIMENS OR DATA PROVIDED BY AN OUTSIDE COLLABORATOR

- A. Research involves **identifiable** data/specimens, or the NIH can link the data/specimens to an individual.

This scenario is characterized as human subjects research and must comply with 45 CFR 46 and be approved by either an NIH IRB and/or an IRB at another institution. If the research is approved at the IRB of another institution, the NIH and that institution must enter into an authorization (reliance) agreement, discussed in SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH.

- B. The research is **not FDA-regulated and is** performed at the NIH on specimens/data that have been **de-identified**. Typically, the collaborations involve the following scenarios:
 1. The outside **collaborator** is conducting an ongoing study and will provide coded specimens/data for which the results are sought

2. The collaborator is providing coded specimens/data but does not wish any results to be returned
3. The collaborator will provide archived specimens/data.

These cases may not be considered engagement in human subjects research on the part of the NIH researcher. The NIH researcher must obtain a determination from the Office of Human Subjects Research Protections (OHSRP)/IC designee before the research begins. The collaborator may need IRB approval and an FWA at his/her institution. (See SOP 5 – Required Review for NIH Research Activities with Human Subjects and Specimens/Data and SOP 6 – Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP) to understand more about the NIH requirements for approval of this research.)

20.5.2 THE NIH RESEARCHER WILL INTERACT DIRECTLY WITH HUMAN SUBJECTS AT ANOTHER INSTITUTION UNDER A NON-NIH APPROVED PROTOCOL

The NIH is engaged in Human Subjects Research. The NIH researcher must either: submit the protocol for approval to an NIH IRB or enter into an Authorization (Reliance) Agreement between NIH and the other institution to rely on the IRB of that institution.

Activities of the NIH researcher must be set forth in the IRB-approved protocol at the other institution and the other institution must hold an active FWA; NIH IRB approval must be sought or a Reliance Agreement established by request through OHSRP.

Applicable SOP: SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH discusses the reasoning and the process for obtaining a reliance agreement at the NIH.

Engagement with human subjects at non-NIH facilities is not permitted as part of NIH approved duties for Intramural Research Training Awardees or other non-Employee trainees unless approved by OIR/DDIR.

20.5.3 AN NIH RESEARCHER IS A PI ON AN NIH IRB-APPROVED PROTOCOL THAT IS IMPLEMENTED AT A NON-NIH SITE; FOR EXAMPLE, NIH PROTOCOLS THAT ARE ADMINISTERED AT A LOCAL HOSPITAL OR OVERSEAS

If the staff of the other site is also engaged in the Human Subjects Research, the site must either provide local IRB review at that institution or a Reliance Agreement must be sought via OHSRP for that institution to rely on the NIH IRB.

Applicable SOP: SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH discusses the reasoning and the process for obtaining a reliance agreement at the NIH.

20.5.4 AN NIH PI IS AN INVESTIGATOR IN A MULTI-SITE PROTOCOL

If an NIH PI is an investigator in a multi-site protocol and the NIH serves as the **Central** IRB, the NIH will review and provide oversight for this research. The other sites have the option of relying on the NIH IRB or must provide local IRB review. If another site has an IRB that is the **Central** IRB for this research, the NIH has the option of relying on that IRB or doing its own IRB review at the NIH.

Applicable SOPs: SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH discusses reliance agreements. SOP 20B – NIH Responsibilities When Reviewing Local Context Considerations for Off-Site Research discusses factors for IRBs to consider when reviewing protocols and providing oversight for sites at locations that are different from that of the IRB. SOP 20B discusses the significance of “local context” and appropriate ways for an NIH IRB to evaluate local context at another geographic location, including international sites.

20.5.5 AN NIH PI IS THE PI FOR A COORDINATING CENTER FOR A MULTI-SITE PROTOCOL, WHETHER OR NOT NIH IS OTHERWISE ENGAGED IN THE RESEARCH

Most coordinating centers have access to identifiable information about research subjects and are therefore engaged in human subjects research. The PI of the coordinating center should obtain IRB approval at the NIH for this activity, even if s/he has no personal interaction with subjects.

Applicable SOP: SOP 20C – Responsibilities When the NIH Intramural Research Program Serves as a Coordinating Center for a Multi-Site Trial **or Serves as the IRB**

of Record for a Non-NIH Coordinating Center discusses the respective responsibilities of coordinating centers and NIH IRBs that review the activities of a coordinating center.

20.5.6 AN INDIVIDUAL WHO IS NOT AN NIH EMPLOYEE IS ENGAGED IN HUMAN SUBJECTS RESEARCH ON A PROTOCOL AT AN NIH SITE

When an individual, not an NIH employee³, is engaged in NIH human subjects research, working on an NIH protocol, at an NIH site, that individual is usually covered by the FWA of the NIH and is viewed the same as an NIH employee with respect to IRB approval at the NIH.

Applicable SOP: SOP 20D – NIH FWA Coverage for Non-NIH Employees Working on NIH Protocols.

20.5.7 AN NIH PROTOCOL REQUIRES RESEARCH INTERVENTIONS TO BE ADMINISTERED BY DOCTORS IN THE GEOGRAPHIC AREA OF THE RESIDENCES OF NIH SUBJECTS. NON-NIH OUTSIDE PHYSICIANS WILL PERFORM THAT WORK

If the outside doctor works at an institution with an FWA, NIH can enter into a reliance agreement for that institution to rely on the NIH IRB for this research at the other site. If the other site does not have an FWA, the NIH can extend its FWA to that physician through an Individual Investigator agreement.

Applicable SOPs: SOP 20A – Obtaining a Reliance (Authorization) Agreement at the NIH” regarding reliance agreements or SOP 20D – NIH FWA Coverage for Non-NIH Employees Working on NIH Protocols.

20.5.8 A FORMER NIH STAFF MEMBER WHO WANTS TO REMAIN AS AN AI ON AN NIH PROTOCOL AND ONLY CONDUCT ANALYSIS OF IDENTIFIABLE DATA WHILE AT A NON-NIH SITE

When required criteria are met as per SOP 20D, certain former NIH staff may be covered by the NIH FWA. See SOP 20D- NIH FWA Coverage for Non-NIH Employees Working on NIH Protocols.

³ Non-NIH Employees include Adjunct Principal Investigators, Guest Researchers, Special Volunteers, contractors, Intramural Research and Cancer Research Training Awardees and collaborators from academia and industry when not an Intergovernmental Personnel Act appointee. Special Government Employees or Intergovernmental Personnel Act appointees are viewed the same as NIH employees for the purposes of this SOP.

Applicable SOP: SOP 20D – Collaborations Involving Non-NIH Employees Working on NIH Protocols. Applicable agreement: NIH FWA Coverage Agreement (see SOP 20D – Collaborations Involving Non-NIH Employees Working on NIH Protocols).

REFERENCES

OHRP Guidance on Engagement of Institutions in Human Subjects Research:
<http://www.hhs.gov/ohrp/policy/engage08.html>

LIST OF APPENDICES

Appendix A: OHRP Guidance on Engagement of Institutions in Human Subjects Research

APPENDIX A: OHRP GUIDANCE ON ENGAGEMENT OF INSTITUTIONS IN HUMAN SUBJECTS RESEARCH

Date: October 16, 2008

NOTE: This guidance document replaces two previous OHRP guidance documents: (1) “Engagement of Institutions in Research” (January 26, 1999); and (2) “Engagement of Pharmaceutical Companies in HHS-Supported Research (PDF)” (December 23, 1999).

This guidance represents OHRP’s current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

Scope: This guidance document applies to research involving human subjects that is conducted or supported by the Department of Health and Human Services (HHS). When an institution is *engaged* in non-exempt human subjects research that is conducted or supported by HHS, it must satisfy HHS regulatory requirements related to holding an assurance of compliance and certifying institutional review board (IRB) review and approval. This guidance document describes:

1. scenarios that, in general, would result in an institution being considered engaged in a human subjects research project;
2. scenarios that would result in an institution being considered not engaged in a human subjects research project; and
3. IRB review considerations for cooperative research in which multiple institutions are engaged in the same non-exempt human subjects research project.

The scenarios below of situations where an institution is generally considered to be *engaged* or *not engaged* in human subjects research conducted or supported by HHS apply to all types of institutions, including academic or other non-profit organizations, institutions operating commercial repositories, and pharmaceutical or medical device companies.

Target Audience: IRBs, research administrators and other relevant institutional officials, investigators, and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

I. Background

Before engaging in HHS-conducted or -supported human subjects research that is not exempt under HHS regulations at 45 CFR 46.101(b), an institution must:

1. hold or obtain an OHRP-approved Federalwide Assurance (FWA) [45 CFR 46.103(a)]; and,
2. certify to the HHS agency conducting or supporting the research that the research has been reviewed and approved by an IRB designated in the FWA and will be subject to continuing review by an IRB [45 CFR 46.103(b)].

Note that the IRBs designated under an FWA may include IRBs of other institutions or independent IRBs. For more information on FWAs and how to designate an IRB of another institution on an FWA, see the following:

- OHRP Assurances Webpage
(<http://www.hhs.gov/ohrp/assurances/index.html>)
- OHRP FWA Frequently Asked Questions
(<http://answers.hhs.gov/ohrp/categories/1565>),
- OHRP Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction of the Individual Investigator Agreement
(<http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html>), and
- OHRP IRB Registration Frequently Asked Questions
(<http://answers.hhs.gov/ohrp/categories/1565>).

The following definitions are relevant for determining whether an institution's activities are covered by the HHS protection of human subjects regulations (45 CFR part 46), and whether the institution is engaged in human subjects research.

Research is defined in 45 CFR 46.102(d) as follows:

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.

Human subject is defined in 45 CFR 46.102(f) as follows:

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.

Institution is defined in 45 CFR 46.102(b) as any public or private entity or agency (including federal, state, and other agencies).

For purposes of this document, an institution's *employees or agents* refers to individuals who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. "Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

II. When to Use This Guidance

This guidance should only be applied to activities that have been determined to be research involving human subjects that are not exempt under HHS regulations at 45 CFR 46.101(b). The following guidance documents available on the OHRP website may be helpful in determining whether research involves human subjects and also whether it is exempt: [OHRP Human Subject Regulations Decision Charts](#) (see [OHRP Guidance on Research Involving Coded Private Information or Biological Specimens](#) (PDF) (see <http://www.hhs.gov/ohrp/policy/cdebiol.pdf>).

Once an activity is determined to involve non-exempt human subjects research, this guidance should be used to determine whether an *institution* involved in some aspect of the research is *engaged* in that human subjects research, because if it is, certain regulatory requirements apply. Specifically, institutions that are engaged in non-exempt human subjects research are required by 45 CFR part 46 to:

1. hold or obtain an applicable OHRP-approved FWA [45 CFR 46.103(a)]; and
2. certify to the HHS agency conducting or supporting the research that the research has been reviewed and approved by an IRB designated in the FWA, and will be subject to continuing review by an IRB [45 CFR 46.103(b)].

OHRP recognizes that many institutions and individuals (e.g., the principal investigator, statistical centers, community physicians, educators, data repositories) may work together on various aspects of a human subjects research project. However, not all participating institutions and individuals need to be covered by an FWA or certify IRB review and approval of the research to the HHS agency conducting or supporting the research. This guidance aims to assist institutions in determining whether they must meet those requirements, that is, whether they are *engaged* in activities covered by the regulations.

III. Interpretation of Engagement of Institutions in Human Subjects Research

In general, an institution is considered *engaged* in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. The following two sections apply these concepts.

The scenarios in Section A describe the types of institutional involvement that generally would result in an institution being engaged in human subjects research. The scenarios in Section B include the types of institutional involvement that would result in an institution being **not** engaged in human subjects research, but these scenarios are not intended to be all-inclusive. There may be additional scenarios in which an institution would be **not** engaged in human subjects research. The determination of engagement depends on the specific facts of a research study and may be complex.

In applying this guidance, it is important to note that at least one institution must be determined to be engaged in any non-exempt human subjects research project that is conducted or supported by HHS (45 CFR 46.101(a)).

In the scenarios below, employees and agents are individuals acting on behalf of the institution, exercising institutional authority or responsibility, or performing institutionally designated activities.

A. Institutions Engaged in Human Subjects Research

In general, institutions are considered *engaged* in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would need to hold or obtain OHRP-approved FWAs and certify IRB review and approval to HHS) when the involvement of their employees or agents in that project includes any of the following:

- A. Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.
- B. Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.

Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures.

[See scenarios B.(1), B.(2), and B.(3) below for limited exceptions.]

- C. Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.

Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions.

[See scenarios B.(1) and B.(3) below for limited exceptions.]

- D. Institutions whose employees or agents interact for research purposes with any human subject of the research.

Examples of interacting include engaging in protocol dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires.

[See scenarios B.(1), B.(2), B.(3), and B.(4) below for limited exceptions.]

- E. Institutions whose employees or agents obtain the informed consent of human subjects for the research.
- F. Institutions whose employees or agents **obtain** for research purposes identifiable private information or identifiable biological specimens **from any source** for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:
 - a. observing or recording private behavior;
 - b. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
 - c. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding

systems.

[See scenarios B.(1), B.(2), B.(3), B.(7), B.(8), B.(9), and B.(10) below for limited exceptions.]

B. Institutions Not Engaged in Human Subjects Research

Institutions would be considered **not** engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is **limited to one or more** of the following. The following are scenarios describing the types of institutional involvement that would make an institution **not** engaged in human subjects research; there may be additional such scenarios:

1. Institutions whose employees or agents perform commercial or other services for investigators provided that **all** of the following conditions also are met:
 - a. the services performed do not merit professional recognition or publication privileges;
 - b. the services performed are typically performed by those institutions for non-research purposes; and
 - c. the institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol.

The following are some examples, assuming the services described would not merit professional recognition or publication privileges:

- an appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for investigators as a commercial service.
- a transcription company whose employees transcribes research study interviews as a commercial service.
- a hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to investigators as a service.

- a radiology clinic whose employees perform chest x-rays and send the results to investigators as a service.
2. Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that **all** of the following conditions also are met:

the institution's employees or agents **do not** administer the study interventions being tested or evaluated under the protocol;

- a. the clinical trial-related medical services are typically provided by the institution for clinical purposes;
- b. the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and
- c. when appropriate, investigators from an institution engaged in the research retain responsibility for:
 - i. overseeing protocol-related activities; and
 - ii. ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

Note that institutions (including private practices) not initially selected as research sites whose employees or agents administer the interventions being tested or evaluated in the study—such as administering either of two chemotherapy regimens as part of an oncology clinical trial evaluating the safety and effectiveness of the two regimens—generally would be engaged in human subjects research (see scenario B.(3) below for a limited exception). If such an institution does not have an FWA, its employees or

agents may be covered by the FWA of another institution that is engaged in the research through an Individual Investigator Agreement. See <http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf>.

3. Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (e.g., an oncologist at the institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that **all** of the following conditions also are met:
 - a. an investigator from an institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol;
 - b. the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;
 - c. investigators from the institution engaged in the research retain responsibility for:
 - i. overseeing protocol-related activities;
 - ii. ensuring the study interventions are administered in accordance with the IRB-approved protocol; and
 - iii. ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; **and**
 - d. an IRB designated on the engaged institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution **not** selected as a research site.
4. Institutions whose employees or agents:
 - a. inform prospective subjects about the availability of the research;

- b. provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects' consent for the research or act as representatives of the investigators;
- c. provide prospective subjects with information about contacting investigators for information or enrollment; and/or
- d. seek or obtain the prospective subjects' permission for investigators to contact them.

An example of this would be a clinician who provides patients with literature about a research study at another institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient's name and telephone number to investigators.

- 5. Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another institution.

Examples would be a school that permits investigators from another institution to conduct or distribute a research survey in the classroom; or a business that permits investigators from another institution to recruit research subjects or to draw a blood sample at the work site for research purposes.

- 6. Institutions whose employees or agents **release** to investigators at another institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research.

Note that in some cases the institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the institution releasing such information or specimens should:

- a. ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or

- b. if informed consent was waived by the IRB, ensure that the release would be consistent with the IRB's determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d).

Examples of institutions that might release identifiable private information or identifiable biological specimens to investigators at another institution include:

- a. schools that release identifiable student test scores;
- b. an HHS agency that releases identifiable records about its beneficiaries; and
- c. medical centers that release identifiable human biological specimens.

Note that, in general, the institutions whose employees or agents **obtain** the identifiable private information or identifiable biological specimens from the releasing institution would be engaged in human subjects research. (See scenario A.(6) above.)

7. Institutions whose employees or agents:
 - a. obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and
 - b. are **unable** to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:
 - the institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to the those employees or agents under any circumstances;
 - the releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution's employees or agents under any circumstances; or
 - there are other legal requirements prohibiting the release of the key to the institution's employees or agents.

For purposes of this document, *coded* means that:

- a. identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); and
- b. a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Although this scenario resembles some of the language in OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens, it is important to note that OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens addresses when research involving coded private information or specimens is or is not research involving *human subjects*, as defined in 45 CFR 46.102(f) (see <http://www.dhhs.gov/ohrp/policy/cdebiol.pdf>). As stated above in Section II., this Guidance on Engagement of Institutions in Human Subjects Research should only be applied to research projects that have been determined to involve human subjects and that are not exempt under HHS regulations at 45 CFR 46.101(b).

8. Institutions whose employees or agents access or utilize individually identifiable private information **only** while visiting an institution that is engaged in the research, provided their research activities are overseen by the IRB of the institution that is engaged in the research.
9. Institutions whose employees or agents access or review identifiable private information for purposes of study auditing (e.g. a government agency or private company will have access to individually identifiable study data for auditing purposes).
10. Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.
11. Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

IV. IRB Review Considerations for Cooperative Research

OHRP notes that multiple institutions may be engaged in the same non-exempt human subjects research project. For such cooperative research projects, institutions may enter into joint review arrangements, rely upon the review of another qualified IRB, or make

similar arrangements to avoid duplication of effort, in accordance with HHS regulations at 45 CFR 46.114.

When an institution is engaged in only part of a cooperative research project along the lines of scenarios A.(2), A.(3), A.(4), A.(5), or A.(6), the institution must ensure that the IRB(s) designated under its FWA reviews and approves the part(s) of the research in which the institution is engaged. For example, an institution operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions must ensure that an IRB designated under its FWA reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center. In such a case, the IRB should ensure that the statistical center has sufficient mechanisms in place to adequately protect the privacy of subjects and maintain the confidentiality of the data. When an institution is engaged in only part of a cooperative research project, the reviewing IRB may decide to review the entire research study, even if information about the entire study is not necessary to approve the institution's part of the research under 45 CFR 46.111.

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 447-4777 (toll-free within the U.S.) or (240) 453-6900, or by e-mail at ohrp@hhs.gov⁴.

⁴ <http://www.hhs.gov/ohrp/policy/engage08.html> downloaded 7/2/2013