

Engagement of Institutions in Human Subjects Research (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.

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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:

- o [OHRP Assurances Webpage](#)
- o [OHRP FWA Frequently Asked Questions](#)
- o [OHRP Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction of the Individual Investigator Agreement](#) , and
- o [OHRP IRB Registration Frequently Asked Questions](#)

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. (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](#)).

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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:

1. 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.
2. 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.]

3. 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.]

4. 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.]

5. Institutions whose employees or agents obtain the informed consent of human subjects for the research.

6. 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:

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

- a. the institution's employees or agents **do not** administer the study interventions being tested or evaluated under the protocol;
- b. the clinical trial-related medical services are typically provided by the institution for clinical purposes;
- c. the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and
- d. 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/regulations-and-policy/guidance/extension-of-institutional-fwa-via-individual-investigator-agreement/index.html>.

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). 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.gov.

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