DRAFT

Office for Human Research Protections (OHRP)

Department of Health and Human Services

OHRP Guidance on Engagement of Institutions in Human Subjects Research

NOTE: This draft guidance document would replace two previous OHRP guidance documents: (1) "Engagement of Institutions in Research" (January 26, 1999); and (2) "Engagement of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

This guidance when finalized will represent 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Scope: This draft guidance document applies to research involving human subjects that is conducted or supported by the Department of Health and Human Services (HHS).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 This draft guidance document provides**:** (1) examples of activities that, in general, would result in an institution being considered *engaged* in a human subjects research project, and (2) examples of activities that, in general, would result in an institution being considered *not engaged* in a human subjects research project.

The examples below of situations where an institution is 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, free-standing or 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. Regulatory Background

Before engaging in HHS-conducted or -supported human subjects research that is not exempt under HHS regulations at 45 CFR 46.101(b) (see OHRP Human Subject Regulations Decision Charts [hyperlink to: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm]), 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 application or proposal for 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) and (f)].

Note that the IRBs designated under an FWA may include IRBs of other institutions or independent IRBs.

For more information on FWAs, see http://www.hhs.gov/ohrp/assurances/assurances_index.html

HHS regulations define *research* at 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.

HHS regulations define *human subject* at 45 CFR 46.102(f) as follows:

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

II. When to Use This Guidance

This guidance 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). Institutions should first determine if they are conducting research that involves human subjects and subsequently if the research involving human subjects is non-exempt. 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 and OHRP Guidance on Research Involving Coded Private Information or Biological Specimens.

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 application or proposal for 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) and (f)].

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 human subjects research. 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; or (2) identifiable private information about the subjects of the research [45 CFR 46.102(d),(f)].

It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens from other institutions for the purposes of a non-exempt human subjects research project, without directly interacting with human subjects, still are considered engaged in human subjects research. *Obtaining* identifiable private information means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtain* to include an investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

The following two sections apply these concepts and provide examples of when an institution is *engaged* (Section A) or is *not engaged* (Section B) in human subjects research. Note that the examples below are not intended to be all-inclusive. There may be additional scenarios in which an institution would be either engaged or not engaged in human subjects research.
In the following examples employees and agents, including students, are individuals performing institutionally designated activities and acting on behalf of the institution or exercising institutional authority or responsibility.

A. Examples of 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 the human subjects research includes any of the following activities:

(1) Institutions that receive support directly from HHS for non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out by agents or employees of another institution. For example, if the direct awardee subcontracts all human subjects research activities supported by an award to another institution, the awardee institution would still be considered engaged in the research.

(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 psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures. [See example B.(4) and (7) 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.

(4) Institutions whose employees or agents interact for research purposes with any human subject.

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; conducting research interviews or administering questionnaires; and obtaining informed consent. [See example B.(5) and (7) below for limited exceptions.]

(5) Institutions whose employees or agents **obtain** for research purposes identifiable private information or identifiable biological specimens **from any source**. Obtaining includes, but is not limited to:

(a) observing and/or recording private behavior; and
(b) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the employees or agents of the institution.

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 examples B.(2), (3), (9), and (10) for limited exceptions.]

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 such a cooperative research project along the lines of example A(1)

above, the awardee institution must ensure that the IRB(s) designated under its FWA review and approve the entire research project.

When an institution is engaged in a component of a cooperative research project along the lines of examples (A)(2), (3), (4), or (5), the institution must ensure that the IRB(s) designated under its FWA reviews and approves the component(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.

B. Examples of Institutions Not Engaged in Human Subjects Research

In general, 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 the human subjects research is limited to one or more of the following activities. It is important to remember that if an institution's employees or agents are involved in any of the activities listed below but are also involved in any of the activities under Section A, then the institution is engaged in the human subjects research project. The following are examples of activities that would not make an institution engaged in human subjects research:

(1) 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. For example, 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 the institutions whose employees or agents will receive the identifiable private information or identifiable biological specimens will be engaged in human subjects research. [See example A.(5) above.]

(2) Institutions whose employees or agents consult or collaborate on the human subjects research by obtaining coded private information or human biological specimens from an institution engaged in the research that retains a link to individually identifying

information (such as name or social security number), if one of the following conditions is met:

(a) the key to decipher the code is destroyed before the consultants or collaborators obtain the coded private information or specimens;
(b) the consultants or collaborators and the holder of the key enter into an agreement prohibiting the release of the key to the consultants or collaborators under any circumstances;
(c) 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 consultants or collaborators under any circumstances; or
(d) there are other legal requirements prohibiting the release of the key to the consultants or collaborators.

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.

(3) Institutions whose employees or agents consult or collaborate on human subjects research conducted at another institution that is engaged in the research, and:

(a) the consultants or collaborators access or utilize individually identifiable private information **only** while at the institution that is engaged in the research; and,

(b) the consultants' or collaborators' research activities are overseen by the IRB of the institution that is engaged in the research.

(4) Institutions whose employees or agents perform commercial or non-collaborative services for investigators that are typically performed by those institutions for non-research purposes. For example, an appropriately qualified laboratory performs routine serum chemistry analyses of blood samples for investigators solely on a commercial basis.

(5) Institutions whose employees or agents:

(a) inform prospective subjects about the availability of research;
(b) provide prospective subjects with information about research (which may include a copy of the relevant informed consent document and other IRB-approved materials) but do not obtain subjects' consent 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.

(6) 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.

(7) Institutions (including private practices) not selected as research sites whose employees or agents administer clinical trial-related medical services if all of the following conditions are met:

(a) the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for research participation;
(b) the institution's employees or agents do not administer **the primary study interventions being tested under the protocol**;
(c) the institution's employees or agents provide only services that either are clinically indicated or are dictated by the protocol, but not clinically indicated, 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, such as a blood test, chest X-ray, CT scan, medical history and physical examination, or an assessment and reporting of an adverse event;
(d) the investigator(s) from an institution engaged in the research retain responsibility for oversight of all protocol-related activities and assure that appropriate arrangements are made for any safety monitoring and adverse event reporting required under the IRB-approved protocol;
(e) when appropriate, the informed consent document states that follow-up data are to be provided to the investigators by the institution's employees or agents; and
(f) when providing follow-up data to the investigators, the institution's employees or agents provide such data to the investigators in accord with the procedures described in the informed consent.

Note that institutions (including private practices) not selected as research sites whose employees or agents administer the primary study interventions being tested in the study— such as administering a cycle of experimental chemotherapy or experimental radiation treatment as part of an oncology clinical trial evaluating the safety and effectiveness of such chemotherapy or radiation treatment—would be engaged in human subjects research. Such investigators may be covered by the FWA of an institution that is engaged in the research through an Individual Investigator Agreement. See http://www.hhs.gov/ohrp/humansubjects/assurance/guidanceonalternativetofwa.pdf

(8) Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

(9) Institutions whose employees or agents access or review identifiable private information for purposes of study auditing, if the IRB-approved protocol and informed consent document clearly describe this practice.

(10) Institutions whose employees or agents receive identifiable private information for purposes of satisfying FDA reporting requirements, if the IRB-approved protocol and informed consent document clearly describe this practice.

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.