DRAFT

Office for Human Research Protections (OHRP)

Department of Health and Human Services (HHS)

Guidance on Important Considerations for When Participation of Human Subjects in Research is Discontinued

This draft guidance, when finalized, will represent OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are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.

Date: November 7, 2008 (DRAFT)

Scope: This document applies to non-exempt human subjects research conducted or supported by HHS. It provides guidance on important considerations for when participation of human subjects in research is discontinued, either because a subject voluntarily chooses to discontinue

participation during the course of the research, or because an investigator terminates a subject's participation in the research without regard to the subject's consent. In particular, OHRP offers guidance on the following topics:

I. What does the word *participation,* as used in HHS regulations at 45 CFR part 46, subpart A, mean?

II. What does *discontinuation of a subject's participation* in research mean?

III. The distinction between a c*omplete* versus a p*artial* discontinuation of a subject's participation in research.

IV. Clarification that investigators may continue to analyze already collected individually identifiable private information about a subject even when the subject's participation has been completely discontinued.

V. Considerations regarding the discontinuation of a subject's participation in emergency research for which the requirements for obtaining informed consent were waived by the IRB.

VI. Clarification that research can continue to involve human subjects even when the participation of all subjects has been completed or discontinued.

VII. Recommendations for documenting the discontinuation of subjects' participation in research.

For HHS-conducted or supported research that is regulated by the Food and Drug Administration (FDA), you also should refer to FDA's guidance on this issue.

[NOTE: OHRP notes that the FDA has issued a related final guidance document entitled "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials." OHRP believes the interpretations provided in the proposed draft guidance below are harmonious with those provided in FDA's final guidance document. In particular, FDA's guidance document explains that under applicable FDA law and regulations, data collected on study subjects enrolled in an FDA-regulated clinical trial up to the time of subject withdrawal must remain in the trial database in order for the study to be scientifically valid. Likewise, OHRP's proposed draft guidance clarifies that when a subject informs an investigator of his/her decision to discontinue participation in research, or an investigator decides to terminate a subject's participation regardless of the subject's consent, the investigator may continue to analyze already collected individually identifiable private information about that subject. In addition, OHRP believes that its proposed draft guidance document is consistent with the HIPAA Privacy Rule (45 CFR part 160 and Subparts A and E of 56 CFR part 164), where applicable. The Privacy Rule gives an individual the right to revoke Authorization in writing, except to the extent a covered entity has taken action in reliance on the Authorization. In the context of research, this reliance exception permits the continued use and

disclosure of protected health information already obtained pursuant to the Authorization prior to its revocation, to the extent necessary to protect the integrity of the research study.]

Target Audience: Institutional review boards (IRBs), investigators, and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

A. Definition of a *Human Subject*

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:
>
> (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.

B. Pertinent Requirements for Obtaining Informed Consent Under the HHS Regulations at 45 CFR Part 46, Subpart A

HHS regulations at 45 CFR 46.116 stipulate that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representatives. HHS regulations at 45 CFR 46.102(c) define *legally authorized representative* as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the research.

HHS regulations at 45 CFR 46.116(a) require that in seeking informed consent investigators must provide each subject with the following, among other things:

- An explanation of the expected duration of participation (45 CFR 46.116(a)(1)); and
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116(a)(8)).

HHS regulations at 45 CFR 46.116(b) require that in seeking informed consent investigators, when appropriate, must provide each subject with the following, among other things:

- A description of the anticipated circumstances under with the subject's participation may be terminated by the investigator without regard to the subject's consent (45 CFR 46.116(b)(2));
- A description of any additional costs to the subject that may result from participation in the research (45 CFR 46.116(b)(3));
- A description of the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject (45 CFR 46.116(b)(4)); and

- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject (45 CFR 46.116(b)(5)).

An IRB may waive some or all of the above informed consent requirement in accordance with either the requirements of HHS regulations at 45 CFR 46.116(c) or (d) or the requirements of the HHS Secretarial waiver of the general requirements for obtaining informed consent for a limited class of research in emergency settings (see section C below). In order for an IRB to waive some or all of the above informed consent requirements, it must find and document, among other things, that whenever appropriate, the subjects will be provided with additional pertinent information after participation.

C. Pertinent Requirements for Waiver of Informed Consent for Certain Emergency Research

On October 2, 1996, the Secretary of Health and Human Services waived the applicability of the requirements for obtaining and documenting informed consent under 45 CFR 46.116 and 46.117, respectively, in accordance with the requirements of HHS regulations at 45 CFR 46.101(i) (see 61 FR 51531-51533 at http://www.hhs.gov/ohrp/documents/100296.pdf). This Secretarial waiver applies to a strictly limited class of HHS-conducted or –supported research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be

obtained. In order for this waiver to be implemented, the IRB must ensure that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research, and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible.

D. IRBs May Use an Expedited Review Procedure When Conducting Continuing Review of Research that Involves no More Than Minimal Risk and Only Data Analysis

HHS regulations at 45 CFR 46.109(e) require that an IRB conduct continuing review of non-exempt human subjects research at intervals appropriate to the degree of risk, but not less than once per year.

Under HHS regulations at 45 CFR 46.110(b)(1), an IRB may use an expedited review procedure for initial or continuing review of some or all of the research appearing on the list of categories published by the Secretary, HHS (see the November 9, 1998 list of Categories of Research That

May Be Reviewed by the IRB through an Expedited Review Procedure on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm) and found by the reviewer(s) to involve no more than minimal risk. Category 8(c) from the November 9, 1998 list involves continuing review of research previously approved by the convened IRB where the remaining research activities are limited to **data analysis**.

Guidance:

For a variety of reasons, a subject enrolled in a research project may inform an investigator of his/her decision to discontinue participation in the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. In these circumstances, questions sometimes arise about (1) whether the investigator may continue to use, study, or analyze already collected data about the subject (or already collected biological specimens originating from the subject) whose participation has been discontinued or terminated, and (2) whether the investigator can continue to collect data about the subject or biological specimens originating from the subject, and if so, under what circumstances. The answers to these questions depend upon the interpretation of the definition of *human subject* at 45 CFR 46.102(f) and of the word *participation* as it is used in HHS regulations at 45 CFR part 46, subpart A.

The guidance below provides OHRP's interpretation of the word *participation*, explains the implications of a subject's decision to discontinue participation in research or an investigator's

decision to terminate a subject's participation in research, and clarifies the distinction between *human subjects research* and a subject's *participation* in such research.

I. What Does the Word *Participation*, as Used in HHS Regulations at 45 CFR Part 46, Subpart A, Mean?

With respect to a particular ongoing non-exempt human subjects research project, OHRP interprets subject *participation* as used in 45 CFR part 46, subpart A to include only one or more of the following activities being performed for research purposes that are described in the IRB-approved protocol:

(1) Interacting or intervening with the subjects (e.g., conducting an interview, drawing a blood sample, administering a study drug);

(2) Collecting individually identifiable private information about the subjects without the investigator interacting or intervening with them (e.g., collecting information about the subjects by reviewing their medical records or their school records);

(3) Collecting individually identifiable biological specimens originating from the subjects without the investigator interacting or intervening with them (e.g., collecting identifiable tissue specimens from clinical specimens stored by the pathology department of a hospital); and

(4) Using or testing individually identifiable biological specimens already collected by the investigator (e.g., performing a genetic test on a tissue specimen already collected from a subject).

In contrast, OHRP interprets subject *participation* as used in 45 CFR 46.116(a)(8) and 46.116(b)(2) **not** to include the following activities:

(1) Any continued analysis by the investigator of individually identifiable private information about the subject that was obtained by the investigator prior to the subject's decision to discontinue participation in a study or prior to an investigator's decision to terminate a subject's participation without regard to the subject's consent, provided the analysis was described in the IRB-approved protocol; and

(2) Any continued analysis by the investigator of data that was derived by an investigator through a previous use or test of a subject's individually identifiable biological specimens prior to the subject's decision to discontinue participation in a study or prior to an investigator's decision to terminate a subject's participation without regard to the subject's consent, provided the analysis was described in the IRB-approved protocol.

II. What Does *Discontinuation of a Subject's Participation in Research* Mean?

A subject may discontinue participation in research at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116(a)(8)). Furthermore, an investigator may terminate a subject's participation in research at anytime without regard to the subject's consent (45 CFR 46.116(b)(2)). Given the scope of the meaning of the word *participation, discontinuation of a subject's participation in research* means discontinuation of one or more of the following activities described in the IRB-approved protocol:

(1) interacting or intervening with the subject;

(2) Collecting individually identifiable private information about the subject without the investigator interacting or intervening with the subject;

(3) Collecting individually identifiable biological specimens originating from the subject without the investigator interacting or intervening with the subject; or

(4) Using or testing individually identifiable biological specimens already collected by the investigator.[1]

III. The Distinction Between a *Complete* Versus a *Partial* Discontinuation of a Subject's Participation in Research

[1] Note that this guidance document is not intended to address circumstances in which subjects request that their previously collected individually identifiable biological specimens that have been stored in a repository for purposes of future unspecified research be destroyed or not used for any further research.

Discontinuation of a subject's participation in research may be complete or partial. A *complete* discontinuation means that all activities described in the IRB-approved protocol involving participation of the subject are discontinued. When a subject chooses to completely discontinue participation in a research study, or an investigator decides to completely terminate a subject's participation in a research study without regard to the subject's consent, the investigator must stop all of the activities that involve participation of that subject in the IRB-approved protocol.

A *partial* discontinuation of a subject's participation in research means discontinuation of some but not all of the activities that involve participation of that subject in the IRB-approved protocol. For example, for certain research projects, particularly clinical trials designed to evaluate the safety and effectiveness of specific interventions in the management of diseases or disorders, subjects on occasion want to discontinue the interventions being evaluated in the projects, but are willing to allow the investigators to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as: (1) collecting data through interaction with the subject (e.g., through follow-up interviews or physical exams); (2) obtaining individually identifiable private information from the subject's medical records or the healthcare providers; or (3) using, testing, or analyzing the subject's individually identifiable biological specimens already collected by the investigator.

When a subject informs an investigator that he or she wants to discontinue participation in the research, OHRP recommends that the investigator ask the subject to clarify whether the subject is requesting to discontinue all types of participation, or just participation that involves specific

interventions or interactions. If the subject's request is limited to discontinuation of specific interventions or interactions, research activities involving other types of participation for which the subject previously gave consent may continue.

Likewise, if an investigator decides to terminate a subject's participation in research without regard to the subject's consent because, for example, of concern that the research interventions are exposing the subject to an unacceptable level of risk, OHRP recommends that the investigator ask the subject whether the subject is willing to continue participation in other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as (1) collecting data through interaction with the subject; (2) obtaining individually identifiable private information from the subject's medical records or the healthcare providers; or (3) using, testing, or analyzing the subject's individually identifiable biological specimens already collected by the investigator. If the subject agrees, research activities involving these other types of participation for which the subject previously gave consent may continue.

IV. Investigators may Continue to Analyze Already Collected Individually Identifiable Private Information About a Subject Even When the Subject's Participation has been Completely Discontinued

When a subject chooses to completely discontinue participation in a research study, or an investigator decides to completely terminate a subject's participation in a research study without

regard to the subject's consent, the investigator may continue to analyze individually identifiable private information about that subject or data that was derived by the investigator through a previous use or test of that subject's individually identifiable biological specimens prior to the subject's decision to discontinue participation in a study or prior to an investigator's decision to terminate a subject's participation without regard to the subject's consent,, provided the analysis of such private information or data was described in the IRB-approved protocol. This is because such activities are excluded from the scope of the meaning of the word *participation*.

For example, consider an IRB-approved research study that involves the following sequential procedures for each subject:

(1) Intervening with the subject by performing a biopsy of a particular type of malignant tumor;

(2) Extracting DNA from the tumor biopsy specimen;

(3) Performing an assay for a specific genetic tumor marker on the extracted DNA;

(4) Collecting information about the status of the subject's tumor annually for 5 years by reviewing the subject's medical records and interviewing the subject; and

(5) Analyzing the individually identifiable genetic tumor marker assay data for all subjects to determine the potential role of the presence of the genetic tumor marker on the progression of that type of malignant tumor.

If a subject enrolled in this research decides to discontinue all participation in the research before undergoing the biopsy procedure, the investigator may not proceed with the biopsy procedure on that subject and may not collect information about the status of the subject's tumor annually.

If a subject decides to discontinue all further participation in the research after undergoing the biopsy procedure but before DNA was extracted from the subject's biopsy specimen, the investigator may not proceed with extracting DNA from the subject's biopsy specimen and may not collect information about the status of the subject's tumor annually.

If a subject decides to discontinue all further participation in the research after undergoing the biopsy and after the investigator has extracted DNA from the subject's biopsy specimen but before the assay for the specific genetic tumor marker has been performed, the investigator may not proceed with performing the assay for the specific genetic tumor marker on the subject's extracted DNA and may not collect information about the status of the subject's tumor annually.

Finally, if the subject decides to discontinue all further participation in the research after undergoing the biopsy and after the investigator has extracted DNA from the biopsy specimen and performed the assay for the specific genetic tumor marker on the subject's extracted DNA,

the investigator may proceed with analyzing the individually identifiable data about the genetic tumor marker results from that subject and any data collected so far about the status of the subject's tumor. However, the investigator may not collect any additional private information about the status of the subject's tumor or disease status while the subject remains alive.

V. Considerations Regarding Discontinuation of a Subject's Participation in Emergency Research for Which the Requirements for Obtaining Informed Consent Were Waived by the IRB

For emergency research not subject to FDA regulations that involves a waiver of the requirements for obtaining the informed consent of subjects in accordance with the October 2, 1996 Secretarial waiver (see 61 FR 51531-51533 at http://www.hhs.gov/ohrp/documents/100296.pdf), investigators at the earliest feasible opportunity must inform each subject enrolled without his or her informed consent (or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member) of certain information. This information must include the following, among other things:

(1) Information about the subject's inclusion in the research;

(2) The details of the research; and

(3) A statement that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

For subjects enrolled in such emergency research without providing informed consent, all of the considerations discussed above regarding discontinuation of a subject's participation in the research apply if a subject (or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member) informs the investigator that the subject's participation is to be discontinued.

VI. Research Can Continue to Involve Human Subjects Even When the Participation of All Subjects has Been Completed or Discontinued

It is important to recognize the distinction between *human subjects research* and a *subject's participation* in such research as discussed above.

OHRP considers a research project to continue to involve *human subjects* as long as the investigators conducting the research continue to 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(f)]. *Obtaining* identifiable private information means receiving or accessing individually identifiable private information or biological specimens for research purposes. OHRP interprets *obtain* to include an investigator's use, study,

or analysis for research purposes of individually identifiable private information or biological specimens already in the possession of the investigator.

As long as a non-exempt human subjects research project continues to involve analysis of individually identifiable private information by the investigator, the research continues to involve human subjects and must undergo continuing review by an IRB at least annually (45 CFR 46.109(e)). Even when the participation of all subjects in a research project has been completed or discontinued, that research project can continue to involve human subjects. For research involving no more than minimal risk, the IRB may use an expedited review procedure when the only remaining human subjects research activity is the analysis of data that includes individually identifiable private information.

VII. Recommendations for Documenting the Discontinuation of Subjects' Participation in Research

OHRP recommends that whenever a subject chooses to discontinue participation in a research study, or an investigator decides to terminate a subject's participation in a research study without regard to the subject's consent, the investigator document this occurrence in the research records. OHRP recommends that such documentation specify the following:

- Whether the discontinuation of the subject's participation resulted from a decision by the subject or by the investigator;

- Whether the discontinuation involves some or all types of participation; and
- The reason for the discontinuation.

Furthermore, OHRP recommends that the discontinuations of a subject's participation be reported to the IRB. Depending on the circumstances, it may be appropriate to submit an individual report of a subject's discontinuation promptly or to document this occurrence in the next continuing review report. For example, it may be appropriate to submit a report of a subject's discontinuation of participation in research promptly if the discontinuation was related to an unanticipated problem involving risks to the subject.

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.), (301) 496-7005, or (240) 453-6900, or by e-mail at ohrp@osophs.dhhs.gov.