

Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues

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 document applies to non-exempt human subjects research conducted or supported by HHS. It clarifies that when a subject chooses to withdraw from (i.e., discontinue his or her participation in) an ongoing research study, or when an investigator terminates a subject's participation in such a research study without regard to the subject's consent, the investigator may retain and analyze already collected data relating to that subject, even if that data includes identifiable private information about the subject. For HHS-conducted or supported research that is regulated by the Food and Drug Administration (FDA), FDA's guidance on this issue also should be consulted. FDA's guidance entitled, "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials" can be found at www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf.

The guidance addresses the following topics:

- A. What does it mean when a subject withdraws from a research study?
- B. May an investigator retain and analyze already collected data about a subject who withdraws from the research or whose participation is terminated by the investigator?
- C. Can investigators honor subjects' requests to have their data destroyed or excluded from any analysis?
- D. Should the withdrawal of a subject from a research study be documented?
- E. What is the relationship of this guidance to FDA's guidance on this issue and to the HIPAA Privacy Rule?

- F. When seeking the informed consent of subjects, what should investigators tell subjects about data retention in the event the subjects withdraw?

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

Regulatory Background:

The following provisions of the HHS regulations for the protection of human subjects at 45 CFR part 46 are pertinent to this guidance:

- The definition of *human subject* at 45 CFR 46.102(f):

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

- (1) data through intervention or interaction with the individual, or
- (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

- The general requirements for informed consent at 45 CFR 46.116(a)(8):

In seeking informed consent investigators must provide each subject with 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.

- The general requirements for informed consent at 45 CFR 46.116(b)(2) and (4):

In seeking informed consent investigators, when appropriate, must provide each subject with (a) a description of the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's

consent, and (b) the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

Guidance:

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from 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 use, study, or analyze already collected data about the subject who withdraws from the research or whose participation is terminated by the investigator; and (2) whether the investigator can continue to obtain data about the subject and if so, under what circumstances. The guidance below addresses these and related questions. OHRP recommends that investigators plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols and informed consent documents.

A. What does it mean when a subject withdraws from a research study?

Subjects have the right to withdraw from (i.e., discontinue participation in) research at anytime (45 CFR 46.116(a)(8)). If a subject decides to withdraw from all components of a research study, the investigator must discontinue all of the following research activities involving that subject's participation in that study (45 CFR 46.116(a)(8)):

- Interacting or intervening with the subject in order to obtain data about him or her for the research study (e.g., administering an experimental drug, performing a tissue biopsy, drawing blood, exposing the subject to visual stimuli on a computer monitor and measuring response times, orchestrating environmental events or social interactions, or conducting ethnographic interviews with the subject);
- Obtaining additional identifiable private information about the subject for the research study by collecting or receiving such information from any source (e.g., obtaining additional information from the subject's education records or medical records, or obtaining biological specimens pertaining to the subject that have been or will be obtained for clinical purposes and stored in a hospital's pathology department or clinical laboratory); and
- Obtaining additional identifiable private information about the subject for the research study by observing or recording private behavior without interacting or intervening with the subject (e.g., recording mother-infant interactions in the home environment using video cameras or monitoring messages posted on an internet forum that is password-protected and accessed by invitation only).

Sometimes, a subject wants to withdraw from the primary interventional component of a study, but is willing to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such

as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social worker. When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue.

Continued participation in secondary components of a research study may be particularly important in clinical trials designed to evaluate the safety and effectiveness of specific interventions in the management of diseases or disorders. For this reason, OHRP recommends that when a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent may continue. OHRP also recommends that the investigator explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.

For example, consider an IRB-approved clinical trial testing the safety and effectiveness of an experimental chemotherapy regimen in patients with lung cancer that involves the following sequential procedures for each subject:

- (1) Intervening with the subject by administering up to six monthly cycles of the experimental chemotherapy regimen;
- (2) Intervening with the subject by performing a chest CT scan immediately following completion of the last chemotherapy cycle and every six months thereafter for the next five years;
- (3) Obtaining information about the subject's health status through interviews and physical examinations immediately following completion of the last chemotherapy cycle and every six months thereafter for the next five years; and
- (4) Analyzing the data that includes identifiable private information about the subject to determine complete and partial response rates of the lung cancer following the experimental chemotherapy.

If a subject informs the investigator that he or she wishes to withdraw from the clinical trial after the second monthly cycle of the experimental chemotherapy regimen because of unacceptable side effects, the investigator may ask the subject if he or she is willing to undergo the follow-up CT scans, interviews, and physical examinations that were described in the IRB-approved protocol and in the informed consent document signed by the subject. If the subject agrees, these follow-up activities involving the subject may continue.

Likewise, if an investigator decides to terminate a subject's participation in a clinical trial without regard to the subject's consent because, for example, of concern that the primary research intervention is 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) obtaining data through interaction with the subject; or (2) obtaining identifiable private information from the subject's medical records or healthcare providers. OHRP also recommends that the investigator explain to the subject the importance of obtaining follow-up safety data about the subject. If the subject agrees, research activities involving these other types of participation for which the subject previously gave consent may continue.

Finally, OHRP recommends that whenever an investigator terminates a subject's participation in research, the investigator explain to the subject the reasons for this action and, as appropriate, other treatment options.

B. May an investigator retain and analyze already collected data about a subject who withdraws from the research or whose participation is terminated by the investigator?

OHRP interprets the HHS regulations at 45 CFR part 46 as allowing investigators to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.¹

C. Can investigators honor subjects' requests to have their data destroyed or excluded from any analysis?

For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, certainly can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis. Nothing in this document is intended to discourage such a practice. For example, an investigator studying social networks in a community may agree to omit all of the data they have collected from a subject of the study at the request of that subject.

D. Should the withdrawal of a subject from a research study be documented?

OHRP recommends that investigators and IRBs consider whether and how the withdrawal of a subject for a research study should be documented. For example, for biomedical research involving more than minimal risk, it may be appropriate for the investigator to document in the research record each instance of a subject's withdrawal. On the other hand, for longitudinal

¹ As long as a non-exempt human subjects research study continues to involve the use, study, or analysis of identifiable private information by the investigators, the research continues to involve human subjects and must undergo continuing review by an IRB at least annually (45 CFR 46.109(e)).

social science studies involving serial surveys of large numbers of subjects, attrition of subjects over time is common, and documenting each withdrawal of a subject may not be useful or appropriate.

For research in which it is determined to be appropriate to document the withdrawal of a subject, such documentation could specify:

- Whether the withdrawal of the subject resulted from a decision by the subject or by the investigator, and the reasons for the withdrawal, if known; and
- Whether the withdrawal was from all components of the research study or just the primary interventional component.

Furthermore, OHRP recommends that IRBs consider whether and how the withdrawal of a subject should be reported to the IRB. While not required under 45 CFR part 46, such reporting to the IRB may be most appropriate for biomedical research involving more than minimal risk. Depending on the circumstances, it may be appropriate to submit an individual report of a subject's withdrawal 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 withdrawal promptly if the withdrawal was related to an unanticipated problem involving risks to the subject.

E. What is the relationship of this guidance to FDA's guidance on this issue and to the HIPAA Privacy Rule?

FDA has issued a related guidance document entitled "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials" (see www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf). OHRP believes the interpretations provided in OHRP's guidance do not conflict with those provided in FDA's guidance document. In particular, FDA's guidance document explains that under applicable FDA law and regulations, data collected on human 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 guidance clarifies that when a subject informs an investigator of his or her decision to withdraw from the research, or an investigator decides to terminate a subject's participation regardless of the subject's consent, the HHS regulations at 45 CFR part 46 allow the investigator to retain and analyze already collected data relating to that subject that has already been obtained and recorded by the investigator, even if that data includes identifiable private information about the subject. Thus, for HHS-conducted or -supported research that is also regulated by FDA, compliance with FDA's requirements regarding data retention when subjects withdraw from the research will not result in any noncompliance with the provisions of HHS regulations for the protection of human subjects (45 CFR part 46) related to discontinuation of subject participation.

In addition, OHRP notes that the HIPAA Privacy Rule (45 CFR part 160 and subparts A and E of 45 CFR part 164) gives an individual the right to revoke authorization for use and disclosure of protected health information (PHI) in writing, except to the extent a covered entity has taken action in reliance on that authorization. In the context of research conducted by an entity subject

to the Privacy Rule, this reliance exception permits the continued use and disclosure of PHI already obtained pursuant to the authorization prior to its revocation, to the extent necessary to protect the integrity of the research study. Thus, for HHS-conducted or –supported research that is also subject to the HIPAA Privacy Rule, if a subject chooses to withdraw from that research and also revokes authorization in writing for continued use or disclosure of his or her PHI that was already obtained in the research, analysis of that PHI may only continue to the extent necessary to protect the integrity of the research study. For FDA-regulated research, retention and analysis of already collected data, including PHI, is always considered necessary to protect the integrity of the research study.

F. When seeking the informed consent of subjects, what should investigators tell subjects about data retention in the event the subjects withdraw?

OHRP recommends that when seeking the informed consent of subjects, investigators explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research. Including this explanation would better inform subjects about what it means that they may “discontinue participation at any time” (45 CFR 46.116(a)(8)). Below are some examples of what such an explanation might include, depending on whether the HHS-conducted or –supported research study is also subject to FDA regulations or the HIPAA Privacy Rule:

- For HHS-conducted or –supported research that is also FDA-regulated, regardless of whether the research is subject to the HIPAA Privacy Rule, the investigator should inform subjects that data collected about the subject up to the time of subject withdrawal will remain in the trial database and be included in the data analysis.
- For HHS-conducted or –supported research that is not FDA-regulated but is covered by the HIPAA Privacy Rule, if the investigator intends to retain and analyze already collected data about the subject after a subject chooses to withdraw from the research, the investigator should inform subjects that if a subject revokes authorization in writing for continued use or disclosure of his or her PHI that was already obtained in the research, analysis of that PHI will continue only to the extent necessary to protect the integrity of the research study.
- For HHS-conducted or –supported research that is not subject to FDA regulations or the HIPAA Privacy Rule, the investigator should inform subjects whether the investigator intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject’s request that the investigator destroy the subject’s data or that the investigator exclude the subject’s data from any analysis.

Additional Information:

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.