Grand Valley State University Human Research Review Committee	
G-8: OHRP and FDA Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues	
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1. What does it mean when a subject withdraws from a research study?

    a. Subjects have the right to withdraw from (i.e., discontinue participation in) research at any time (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)):

        i. 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);
        ii. 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
        iii. 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).

    b. 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.

c. 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:

    i. Intervening with the subject by administering up to six monthly cycles of the experimental chemotherapy regimen;
    ii. 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;
    iii. 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
    iv. 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.

d. 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.

    i. Similarly, 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.

ii. 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.

2. 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?

    a. 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. (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)).

FDA Guidance - Data Retention When Subjects Withdraw from Trials

1. Background

    a. The Federal Food, Drug, and Cosmetic Act (the act) authorizes the study of an investigational product to develop safety and effectiveness data about the product. The act also requires the maintenance of records documenting these data and the submission of certain reports regarding this use to FDA.[2][3] FDA (by delegation from the Secretary) Investigational New Drug (IND) regulations at 21 CFR Part 312, and investigational devices, the Investigational Device Exemptions (IDE) regulations at 21 C FR Part 812. These regulations specify that data collection and maintenance are indispensable requirements when conducting a clinical investigation of an unapproved product.

    b. The investigational new drug provisions of the act condition use of such drugs upon, for example, "the establishment and maintenance of such records, and the making of such implemented these provisions by issuing regulations relating to investigational drugs, the reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b)." 21 USC 355(i)(l)(C).

c. The investigational device provisions similarly require "that the person applying for an exemption for a device assure the establishment and maintenance of such records, and the making of such reports to the Secretary of data obtained as a result of the investigational use of the device during the exemption, as the Secretary determines will enable him to assure compliance with such conditions, review the progress of the investigation, and evaluate the safety and effectiveness of the device." 21 USC 360j(g)(2)(B)(ii).

    i. For example, the IND regulations require investigators "...to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual ad ministered the investigational drug or employed as a control in the investigation" (21 CFR 312.62(b)).

    Similarly, the IDE regulations require an investigator to maintain "Records of each subject's case history and exposure to the device" (21 CFR812.140(a)(3)).

    Additionally, the regulations relating to the submission of marketing applications require the submission of all relevant data in order for FDA to determine whether a product meets the standard for approval. A new drug application (NDA) must include a description and analysis of each clinical pharmacology study and controlled clinical study, a description of each uncontrolled trial, and an integrated summary of all available information about the safety of the drug product (21 CFR 314.50(d)(5)) and "copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not, including patients receiving reference drugs or placebo" (21 CFR 314.50(f)(2)).

    Similarly, an application for premarket approval (PMA) for a device must include "safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient com plaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation" (21 CFR 814.20(b)(6)(ii)).

    Likewise, an application for a biologics license application (BLA) must include data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product is safe, pure, and potent (21 C FR 601.2(a)).

    FDA law and regulations require the collection and maintenance of complete clinical study data. This includes information on subjects who withdraw from a clinical investigation, whether the subject decides to discontinue participation in the clinical trial (21 CFR 50.25(a)(8)) or is discontinued by the investigator because the subject no longer qualifies under the protocol (for example, due to a significant adverse event or due to failure to cooperate with study requirements). FDA

recognizes that a subject may withdraw from a study; however, the withdrawal does not extend to the data already obtained during the time the subject was en rolled. FDA's longstanding policy has been that all data collected up to the point of withdrawal must be maintained in the database and included in subsequent analyses, as appropriate.[4]

d. FDA previously addressed the topic of data withdrawal in the preamble to the 1996 final rule providing an exception from informed consent requirements for emergency research, 21 CFR 50.24. In response to a comment that a subject's legally authorized representative should be allowed to prevent the review of the subject's data, FDA stated: "FDA regulations (see, for example, Sec. 312.62 and Sec. 812.140(a)(3)) require investigators to prepare and maintain adequate case histories recording all observations and other data pertinent to the investigation on each individual treated with the drug or exposed to the device. T he agency needs all such data in order to be able to determine the safety and effectiveness of the drug or device. The fact of having been in an investigation cannot be taken back. Also, if a subject were able to control the use (inclusion and exclusion) of his or her data, and particularly if the clinical investigation were not blinded, the bias potential would be immense. Thus, the agency rejects this comment because it could prevent FDA from learning of an important effect of the product and significantly bias the results of the investigation" ("see comment 95, 61 Federal Register 51498,51519, October 2, 1996). It should be appreciated that FDA's response applies to the most potentially difficult situation, that is, studies involving an exception from the informed consent requirements in which subjects, due to a life threatening medical condition, are unable to provide informed consent to participate in the stud y. Subjects may subsequently withdraw from such studies, but the data collected up to withdrawal may not be removed.

2. FDA Policy

a. Following are key points regarding FDA's policy on the withdrawal of subjects from a clinical investigation, whether the subject elects to discontinue further interventions or the clinical investigator terminates the subject's participation in further interventions:

i. According to FDA regulations, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
ii. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

iii. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

iv. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

Background

1. Research activities involving an individual's participation, as interpreted by the Office of Human Research Protections (OHRP), include one or more of the following activities:

    a. *Interacting or intervening* with a participant in order to obtain data about him/ her for the research study (e.g., administering an experimental drug, performing a tissue biopsy, drawing blood, exposing the participant to visual stimuli on a computer monitor and measuring response times, orchestrating environmental events or social interactions, or conducting ethnographic interviews with the participant);

    b. *Obtaining identifiable private information* about participants from any source (e.g., education or medical records, or biological specimens); or

    c. *Obtaining identifiable private information* about participants by observing or recording private behavior without interacting or intervening with the participant (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).