

FDA & OHRP Guidance on Data Retention and Other Considerations Applicable to Subjects Who Withdraw From Clinical Research

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On December 1, 2008, the Department of Health and Human Services (“HHS”) Office of Human Research Protections (“OHRP”) announced the availability of a Draft “Guidance on Important Considerations for When Participation of Human Subjects in Research is Discontinued” (“OHRP Guidance”).¹ The OHRP Guidance applies to any research involving human subjects that is supported by federal funding or regulated by federal agencies that have adopted the HHS human subject protection regulations at 46 C.F.R. §101, *et seq.* (“Common Rule”), and may include clinical research that also is subject to the FDA Guidance.² Simultaneously, the United States Food and Drug Administration (“FDA”) announced the availability of a related final guidance document for immediate implementation titled “Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials” (“FDA Guidance”).³ The FDA Guidance applies to all clinical research regulated by the FDA including research conducted under an IND or IDE, studies of non-significant risk devices and other research submitted in support of a marketing application or used to support marketing claims for a drug, biologic or medical device.

These guidance documents are significant as they represent the **first formal** public guidance from the agencies and affirm previous informal statements and positions of FDA and OHRP regarding a subject who withdraws from clinical research by choice or who is withdrawn by the investigator.⁴ This Alert provides an overview of the guidance documents and discusses some of the key compliance considerations for sponsors, investigators, institutions, IRBs and other entities involved in clinical research.

The OHRP Guidance is a draft guidance document, subject to a 60-day comment period and issuance of a final guidance document for implementation. Those entities subject to the Common Rule should review the OHRP Guidance to determine whether they wish to provide comments to the OHRP. Information

regarding submission of comments on the OHRP Guidance can be found at: <http://www.hhs.gov/ohrp/requests/>. Comments must be submitted by January 30, 2009.

OVERVIEW

Inclusion in Study Database: Previously Collected Data from Withdrawn Subjects

FDA Guidance

The FDA's Guidance is consistent with FDA's longstanding policy for FDA-regulated trials⁵ that information collected prior to a subject's withdrawal should remain part of the study database to ensure the scientific validity of the research. The FDA Guidance describes current FDA requirements for collection, maintenance and submission to FDA of complete and accurate data regarding clinical investigations⁶ and articulates the FDA's concerns relating to the reliability of study analyses that exclude data for withdrawn subjects. Specifically, the FDA describes its concern that withdrawn subjects are more likely to have experienced adverse events or a failure of efficacy, and the exclusion of their data has an increased probability of introducing bias and negatively impacting the scientific validity of the research.⁷

Citing to international ethical guidance, the FDA Guidance asserts that the scientific validity of study data is also an ethical imperative.⁸ This ethical guidance provides that research that is not scientifically valid fails to offer a potential benefit to justify the risks to human subjects.

OHRP Guidance

The OHRP Guidance describes the manner in which the Common Rule permits an investigator to continue to analyze previously collected data and, under certain circumstances, to collect additional data regarding a subject who withdraws (or is withdrawn by the investigator) from a clinical trial. Regardless of whether a subject's withdrawal constitutes complete or partial discontinuation of participation in the research,⁹ an investigator may continue to analyze data collected from the subject or derived from the subject's biological specimens up to the time of withdrawal without regard to the subject's consent, since OHRP has determined that these activities are not included in the definition of 'participation' in research requiring a subject's consent.¹⁰

While OHRP excludes analysis of previously collected data from the definition of 'participation' in research requiring informed consent, the OHRP Guidance distinguishes the applicability of such activities to the definition of 'human subjects research' requiring IRB approval and continuing review pursuant to HHS regulations.¹¹ OHRP Guidance states that research continues to involve human subjects during any period in which the investigator continues to analyze previously collected data, even if direct interventions with research subjects have ceased. Therefore, such activities

require continuing IRB review at least annually.¹²

The OHRP Guidance specifically addresses the applicability of the HIPAA Privacy Rule¹³ to the continued use of individually identifiable private information regarding a research subject collected prior to a subject's withdrawal from a clinical trial. The HIPAA Privacy Rule permits an individual to revoke authorization for the use of individually identifiable private information in writing.¹⁴ However, there is an exception when a covered entity has taken action in reliance on the authorization.¹⁵ The OHRP Guidance provides that, "[i]n 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." Therefore, OHRP believes that the continued analysis of previously collected data regarding a withdrawn subject is not inconsistent with a covered entity's obligations pursuant the HIPAA Privacy Rule.

Retention and Analysis of Previously Collected Biological Specimens

OHRP Guidance

The OHRP Guidance provides detailed examples to illustrate the circumstances under which data derived from biological specimens may be used when a subject withdraws from clinical research. According to the OHRP Guidance, a biological specimen that was collected, but was not analyzed prior to a subject's withdrawal may **not** be analyzed following a subject's complete withdrawal from a study. OHRP considers such analysis to constitute data collection within the scope of a subject's participation, thereby requiring consent.

FDA Guidance

The FDA Guidance is silent regarding the analysis of previously collected biological specimens. While the FDA Guidance requires the use of **data** collected up to the time of the subject's withdrawal, the FDA Guidance fails to distinguish those instances in which the data sought has not yet been extracted from a biological specimen.

Responding to a Subject's Withdrawal

FDA Guidance

In the FDA Guidance, the FDA recommends that "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."¹⁶ An investigator may request that a subject permit continued data collection following withdrawal from interventional portions of the study. This should include a discussion of any follow-up activities including interviews or collection of data from chart reviews, as well as the maintenance of privacy and confidentiality of the subject's individually identifiable information. If a subject agrees to continued follow-up, informed consent must be obtained using an IRB approved informed consent document unless follow-up activities

after withdrawal were addressed in the original informed consent document.

If a subject withdraws and does not consent to the collection of follow-up data, the investigator is not permitted to access the subject's medical record or other confidential records requiring the subject's consent for study purposes. Nevertheless, study data related to the subject that were collected prior to the subject's withdrawal may be reviewed by the investigator.

OHRP Guidance

When a subject notifies study personnel of his/her intention to discontinue participation in a clinical trial, the OHRP Guidance recommends that the investigator or his/her designee attempt to clarify whether the subject is requesting complete or partial discontinuation of participation. If the subject's intention is to discontinue the intervention(s) under study, an investigator may continue any other research activities involving the subject's participation that are described in the IRB-approved protocol. Similarly, an investigator who discontinues a subject's use of a research intervention(s) should request permission to continue those research activities described in the IRB-approved protocol that do not involve the intervention(s) under study.

A subject's decision to withdraw from a clinical trial should be documented in the study records. The OHRP Guidance recommends that such documentation at least include:

- “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.”¹⁷

A subject's withdrawal from a clinical trial also should be reported to the IRB. An individual report should be submitted promptly “if the discontinuation was related to an unanticipated problem involving risks to the subject.” In other circumstances, the subject's withdrawal may be reported in the next continuing review report.¹⁸

COMPLIANCE CONSIDERATIONS

Each entity engaged in clinical research is responsible for ensuring the scientific validity, ethical soundness, and regulatory compliance of its operations. Entities subject to the FDA Guidance and OHRP Guidance should review and evaluate current operations, processes, policies and compliance infrastructure to determine whether the recommendations set forth in these guidance documents are addressed adequately. Specifically, sponsors, investigators, institutions, IRBs and other entities involved in clinical research should review policies and procedures, training materials and template documents related to protocol development, statistical analysis and informed consent of clinical research subjects to determine whether they comply with these new guidance documents' recommendations. These entities

should consider:

- **Updating applicable policies and procedures** to ensure consistency with the recommendations of FDA and OHRP, as applicable. These may include: policies related to statistical analysis of data from subjects who discontinue participation in a clinical trial; retention and analysis of biological specimens collected from withdrawn subjects; informed consent document development, review or completion; the informed consent process; development of protocol sections regarding informed consent and discontinuation of study subjects; IRB review of initial protocols and informed consent documents; IRB continuing review reports and IRB continuing review of research activities following discontinuation of study subjects.
- **Reviewing informed consent document templates** to ensure that the documents accurately disclose the extent to which subject data will be used in the event a subject withdraws from the research. Entities should consider whether consent to continuing follow-up data collection activities in the event of subject withdrawal should be sought in informed consent documents used to consent subjects for trial participation or whether separate informed consent documents should be developed for use at the time of withdrawal.
- **Providing training** to individuals involved in planning, review, implementation and analysis of clinical trials regarding the recommendations of the FDA Guidance and OHRP Guidance, as applicable, and any updates to template documents, policies, processes and procedures.
- **Submitting comments** to address uncertainties in the OHRP Guidance or in the FDA Guidance. One area for potential comment may include the lack of clarity regarding the treatment biological specimens under the FDA Guidance. While the FDA Guidance is a final guidance document, issued for immediate implementation, the FDA will accept comments on such guidance documents.

Additionally, sponsors of clinical research should consider:

- **Reviewing protocol templates and case report forms** to ensure these documents incorporate additional documentation recommendations for withdrawn subjects, such as reason for withdrawal and whether withdrawal was the decision of the subject or the investigator.
- **Confirming that statistical analysis plans include analysis of data for withdrawn subjects.** While many sponsors may perform intent-to-treat analyses and have procedures in place to interpret or impute missing data from withdrawn subjects, confirmation that statistical analysis plans comply with the recommendations of the FDA guidance may be considered.

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Endnotes

¹ 73 Fed. Reg. 72804 (December 1, 2008).

² 45 C.F.R. §§46.101 and 46.102(e). FDA has developed its own human subject protection regulations at 21 C.F.R. Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards), and has not adopted the Common Rule. While there is significant overlap between the FDA human subject protection regulations and the Common Rule, there are certain differences. See Patricia L. Brent & Lawrence W. Veraglia, Clinical Research Compliance Manual, §2.02 (2008).

³ 73 Fed. Reg. 72807 (December 1, 2008).

⁴ OHRP Guidance at 9, 12; FDA Guidance at 5.

⁵ FDA has long advised “intent-to-treat analyses (analyzing data related to all subjects the investigator intended to treat), and a variety of approaches for interpretation and imputation of missing data have been developed to maintain study validity.” FDA Guidance at 4.

⁶ Regarding data collection and maintenance obligations of investigators, see, e.g., 21 C.F.R. §312.62(b) (requiring adequate and accurate case histories that record all observations and other data

pertinent to the investigation on each individual administered the investigational drug); 21 C.F.R. §812.140(a)(3) (*requiring records of each subject's case history and exposure to the device under study*). Regarding requirements for contents of marketing applications, see, e.g., 21 C.F.R. §§ 312.314.50(d)(5) (*all information about safety*); 314.50(f)(2) (*copies of case report forms for subjects who died or did not complete the study because of an adverse event*); 814.20(b)(6)(ii) (*information regarding subject discontinuation, case report forms for subjects who died or did not complete the study because of an adverse event*); 601.2(a) (*all data derived from nonclinical and clinical studies*).

⁷ FDA Guidance at 4.

⁸ See, e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 Guidance for Industry, “Good Clinical Practice: Consolidated Guidance,” available at <http://www.fda.gov/cder/guidance/959fnl.pdf>; The Nuremberg Code, available at <http://ohsr.od.nih.gov/guidelines/nuremberg.html>; The Declaration of Helsinki (2000) (as amended), available at <http://www.wma.net/e/policy/b3.htm>; The Belmont Report, available at <http://ohsr.od.nih.gov/guidelines/belmont.html>.

⁹ OHRP Guidance at 13. The OHRP Guidance distinguishes a subject's partial discontinuation of participation from complete discontinuation of participation. “A *complete* discontinuation means that all activities described in the IRB-approved protocol involving the participation of the subject are discontinued.” “A *partial* discontinuation of a subject's participation means discontinuation of some but not all activities that involve participation of that subject...[f]or example [subjects may wish to] discontinue the interventions being evaluated...but are willing to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document.”

¹⁰ OHRP Guidance at 15. The same considerations apply to emergency research subject to a waiver of informed consent. Any information collected up to the time a subject withdraws from participation in the emergency research may be included in the study database. OHRP Guidance at 17.

¹¹ 45 C.F.R. §§46.101, 46.102(f), 46.109.

¹² Where continuing analyses involve no more than minimal risk to human subjects, expedited review may be appropriate. OHRP Guidance at 19.

¹³ 45 C.F.R. Part 160; 56 C.F.R. Part 164, Subparts A and E.

¹⁴ 45 C.F.R. 164.508(b)(5).

¹⁵ 45 C.F.R. 164.508(b)(5)(i).

¹⁶ FDA Guidance at 6.

¹⁷ OHRP Guidance at 20.

¹⁸ *Id.*