Guidance for Sponsors, Clinical Investigators, and IRBs

Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials

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Contains Nonbinding Recommendations

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate telephone number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended for sponsors, clinical investigators and institutional review boards (IRBs). It describes the Food and Drug Administration's (FDA) longstanding policy that already-accrued data, relating to individuals who cease participating in a study, are to be maintained as part of the study data. This pertains to data from individuals who decide to discontinue participation in a study, who are withdrawn by their legally authorized representative, as applicable, or who are discontinued from participation by the clinical investigator. This policy is supported by the statutes and regulations administered by FDA as well as ethical and quality standards applicable to clinical research. Maintenance of these records includes, as with all study records, safeguarding the privacy and confidentiality of the subject's information.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

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)

[1] This guidance document was developed by the Good Clinical Practice Program and the Office of the Chief Counsel (OCC), both in the Office of the Commissioner (OC), FDA.

[2] 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 Investigational New Drug (IND) regulations at 21 CFR Part 312, and investigational devices, the Investigational Device Exemptions (IDE) regulations at 21 CFR Part 812. These regulations specify that data collection and maintenance are indispensable requirements when conducting a clinical investigation of an unapproved product.

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 administered 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 CFR 812.140(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 complaints, 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 CFR 601.2(a)).

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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)(1)(C).

[3] 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).

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 enrolled. 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]

III. DISCUSSION

FDA law and regulations recognize that a complete and accurate risk/benefit profile of an investigational product depends upon the data from every subject's experience in the clinical trial. For example, if a subject's data could be withdrawn from a study, a sponsor would not have access to data on adverse events experienced by the subject and would be unable to evaluate whether changes to the protocol or the informed consent documents are needed to ensure the rights, safety, and welfare of other trial subjects.[5]

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[4] 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. The 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 study. Subjects may subsequently withdraw from such studies, but the data collected up to withdrawal may not be removed.

[5] Such review of safety data by sponsors is required by 21 CFR 312.56 and 21 CFR 812.46.

The validity of a clinical study would also be compromised by the exclusion of data collected during the study. There is long-standing concern with the removal of data, particularly when removal is non-random, a situation called "informative censoring." 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.[6] Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study.

There is particular concern with a study's reliability when subjects withdraw their data in a non-random way because they are unhappy with their experience, either because they failed to obtain a desired effect or suffered an adverse event. Loss of these subjects' data could greatly distort effectiveness results and could hide important safety information (for example, toxicity) of a poorly tolerated treatment. Allowing subjects to withdraw data could even provide an opportunity for unscrupulous parties to "improve" study results by selectively encouraging certain subjects to withdraw from a study.

The importance of ensuring the scientific validity of clinical research is reflected not only in FDA's regulations but in international documents and published literature as well. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in which FDA participates, identifies as a principle of good clinical practice that "clinical trials should be scientifically sound."[7] Other international guidance documents include similar statements, such as the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 1, which states "scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit ... "[8]

Published literature on medical research ethics, dating back to the Nuremburg Code of 1947,[9] also emphasizes the importance of scientific validity. As maintained by

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[6] For a discussion of problems presented by missing data in the analysis of clinical trials, please see "Points to Consider on Missing Data" from the Committee for Proprietary Medicinal Products of the European Medicines Agency (EMEA), http://www.emea.europa.eu/pdfs/human/ewp/177699EN.pdf.

[7] http://www.fda.gov/cder/guidance/959fnl.pdf. ICH E6 Guidance for Industry, "Good Clinical Practice: Consolidated Guidance," adopted as official guidance by FDA, Section 2.5.

[8] http://www.cioms.ch/frame_guidelines_nov_2002.htm. These guidelines are published by the Counsel of International Organizations for Medical Sciences (CIOMS). Guideline 11 reiterates this principle.

[9] The Nuremberg Code: http://ohsr.od.nih.gov/guidelines/nuremberg.html

Emanuel, et. al., "For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan."[10] The importance of scientific validity to ethical research is also underscored in modern ethical documents, such as the Declaration of Helsinki[11] and the Belmont Report, issued in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[12]

In summary, data collected on study subjects up to the time of withdrawal must remain in the trial database in order for the study to be scientifically valid. If a subject withdraws from a study, removal of already collected data would undermine the scientific, and therefore the ethical, integrity of the research. Such removal of data could also put enrolled subjects, future subjects, and eventual users of marketed products at an unreasonable risk. Finally, removal of data would fundamentally compromise FDA's ability to perform its mission, to protect public health and safety by ensuring the safety and effectiveness of regulated products.

IV. FDA POLICY

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:

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[10] Emanuel, EJ, Wendler, D, and Grady, C., "What Makes Clinical Research Ethical?" JAMA 283:20 (May 24/31, 2000 2701-11).

[11] "Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation." The Declaration of Helsinki (2000) (as amended 2002, 2004) http://www.wma.net/e/policy/b3.htm.

[12] The Belmont Report addresses the connection between scientific validity and ethics through the Principle of Beneficence. Beneficence has two complementary aspects: maximizing possible benefits and minimizing possible harms. The Report recognizes as one of the components of maximizing benefits, "In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures." http://ohsr.od.nih.gov/guidelines/belmont.html

- 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.

- 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.

- 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).

- 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.