Marshfield Clinic

Withdrawal of Subjects from Research

1. SCOPE

1.1. System-Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. Engage in Research:

- To intervene or interact with human subjects, or obtain private individually identifiable information about human subjects, for purposes of research.

2.2. Human Subject:

- A living individual about whom an investigator conducting research obtains: 1) data through interaction with the individual or 2) identifiable, private information.

2.3. Individually Identifiable Information:

- Data or specimens with information associating them to identifiable living people or their medical information. *Individually identifiable* means the identity of living individuals is, or may readily be, ascertained by the investigator or associated with the information.
  - ◊ Includes circumstances where private information or specimens can be linked to specific individuals by the investigator, either directly or indirectly through coding systems (e.g., medical history number or other code linked to a legend including a direct identifier, such as name). However, OHRP does not ordinarily consider information to be individually identifiable if: (1) the investigator and the holder of individually identifying information sign an agreement prohibiting the release of individually identifying information to the investigator under any circumstances, or (2) there are other legal requirements prohibiting the release of the link to the investigator.

2.4. Research:

- A systematic investigation including research development, testing and evaluation, designed to contribute to generalizable knowledge.

3. RESOURCE GUIDE BODY

This document is intended to guide Marshfield Clinic investigators and researchers when a human subject withdraws from (discontinues participation in) research at Marshfield Clinic. Subject withdrawal occurs when a subject voluntarily withdraws his or her consent to participate in a study, or when a Principal Investigator (PI) ends a subject's study participation.

3.1. Federal Regulations and Guidance

a. Department of Health and Human Services (DHHS)

- 45 CFR 46.116(a)(8) gives human subjects the right to withdraw their informed consent to participate in a research study at any time.

- 45 CFR 46.116(a)(8) and 45 CFR 46.116(b)(2) and (4) require informed consent documents to include certain statements relating to withdrawal. These include statements that participation in the research is voluntary, that participation may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled, a description of any circumstances whereby an investigator may terminate a subject's participation, consequences of withdrawal, and procedures for orderly withdrawal.
- OHRP issued a guidance document, "Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues" (September 2010), which, among other things, identifies what activities must end at the time of withdrawal and the circumstances whereby investigators can continue to analyze previously collected data, or collect additional data, about the subject.
  - The guidance confirms that subjects can withdraw from a primary interventional study component, but continue participating in other study components, such as allowing for follow-up contact or for their individually identifiable information to be collected from their medical records for the research.
  - The guidance also states that whether a subject withdraws from some or all study components, investigators can retain and analyze data collected from the subject up to the time of withdrawal, so long as the analysis is within the scope of the IRB-approved activities and IRB continuing review of the data analysis occurs at least annually.

    OHRP states that it believes that continuing data retention and analysis is not prevented by a subject revoking his or her HIPAA authorization for the use of his or her individually identifiable private information. The guidance explains that the HIPAA Privacy Rule allows for continued use and retention after revocation when a covered entity "has taken action in reliance on the authorization," and continued retention and analysis of data is not inconsistent with the HIPAA Privacy Rule "when necessary to protect the integrity of the research study."

    According to the guidance, a biological specimen collected but 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 informed consent.
  - The guidance states that an institution may choose to honor a subject's request that his or her data be destroyed or excluded from further analysis at withdrawal, but only with agreement from the funding agency, and only if the research is not FDA-regulated.
  - Whenever an investigator withdraws a subject from participation, OHRP suggests that the investigator explain to the subject the reasons for withdrawal.

- OHRP recommends documenting withdrawals, including the reasons therefor, whether the withdrawal is from some or all study components, and when appropriate, whether they are reported to the IRB.

b. Food and Drug Administration (FDA)

- The FDA issued a guidance document, "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Trials" (October 2008) to address the retention of data after a subject voluntarily withdraws, or is withdrawn by a PI, from FDA-regulated research.
  - The guidance states that because FDA regulations, including those for Investigational New Drugs and Investigational Device Exemptions, rely on study information about safety and effectiveness, the FDA requires all data collected on withdrawing subjects to remain as part of the study database or records after withdrawal. The guidance explains that maintaining all collected data ensures clinical study validity and prevents unreasonable risks to enrolled subjects, future subjects, and eventual users of marketed products. The FDA describes its concern that subjects who withdraw from research are more likely to have experienced adverse events or a failure of efficacy, and allowing exclusion of their data would increase the probability of introducing bias, and would negatively impact the scientific validity of the research.
  - The guidance acknowledges that investigators cannot access a withdrawing subject's medical records or other confidential records after withdrawal without obtaining the subject's informed consent or a waiver of informed consent from the IRB.
  - The guidance confirms that an investigator may ask subjects who are withdrawing from an interventional component of a study whether they want to continue participating in follow-up or further data collection for clinical outcome purposes, but they must obtain informed consent for those activities.

3.2. Considering Future Subject Withdrawals When Submitting Studies to MCRF IRB

a. When designing research studies that will require written informed consent from subjects, the PI should include in their IRB applications and informed consent documents a discussion of what withdrawal will mean, and how it will be handled (e.g., data collected to date will be retained).

b. If, once a study commences, a PI finds that he or she is unexpectedly having to withdraw multiple subjects from the research, or that there are an unexpected number of subjects voluntarily withdrawing, he or she should re-evaluate the protocol and determine whether changes are necessary to facilitate subject retention without weakening the scientific integrity of the research.

3.3. Withdrawal of Research Subjects by PI

a. A PI may withdraw (remove) a subject from some or all study components at any time at his or her discretion. Circumstances can include when a subject's safety may be compromised such as when a subject is experiencing related adverse events requiring discontinuation of a test article, when the study is being

closed by the PI or sponsor related to increased risk to participants, or when the subject is non-compliant with required study regimens or procedures.

b. A PI should always inform a subject that he or she has been withdrawn from participation in a study, and the reasons therefor.

3.4. Voluntary Withdrawal By Subjects

a. At any time, a subject can voluntarily withdraw from participation in some or all components of a study for which he or she previously consented to participate.

3.5. What Activities Must End At Time of Withdrawal

a. Generally, when a subject withdraws from a study, or when a PI decides to terminate a subject's participation, the following activities must cease at the time of withdrawal:

- Interactions or interventions with the subject in order to obtain data about him or her for the research.
  - Examples include administering an experimental drug or drawing blood samples.
- Obtaining additional identifiable private information about the subject for the study by collecting or receiving such information from any source (see the exception for continued data analysis with informed consent, as discussed in Section 3.3., below).
  - Examples include obtaining additional information from the subject's medical records, or obtaining biological samples that have been stored in a clinical laboratory that have not yet been analyzed.
- Obtaining additional identifiable private information about the subject for the research by observing or recording private behavior without interacting or intervening with the subject.

3.6. What Activities May Continue After Subject Withdrawal

a. Retaining and Analyzing Previously Collected Data

- FDA-Regulated Research
  - When a subject withdraws from a FDA-regulated research study, or is withdrawn by a PI, the data collected on the subject to the point of withdrawal must remain part of the study records, and cannot be excluded or destroyed at the request of a withdrawing subject.
- Non-FDA-Regulated Research
  - When a subject withdraws from a non-FDA-regulated study, or is withdrawn by a PI, it is recommended that the data collected on the subject to the point of withdrawal remain part of the study records, and not be excluded or destroyed. However, an investigator may decide to destroy data at the request of a withdrawing subject.

b. Continued Participation In Non-Interventional Research Components

- When a subject voluntarily withdraws from a study involving an interventional component, or when a PI withdraws a subject from such components of a study, a subject may consent to continue participating in

other IRB-approved and subject-consented study components, such as continued follow up or data collection. The following must occur:

- The investigator must ask the subject whether he or she wishes to continue participation in non-interventional study components;
- The investigator must discuss the distinctions between the study-related interventions and the non-interventional study components;

- If a subject completely withdraws from all components of a study, the investigator must not access the subject's medical record or other confidential records for purposes of the research.

3.7. Documentation

a. At a minimum, documentation of subject withdrawal should include the date, rationale, and if applicable, what components of the study for which the subject chooses to continue participation.

b. The IRB may require additional documentation on a case-by-case basis.

3.8. Reporting Subject Withdrawals to MCRF IRB

a. At the time of continuing review of ongoing research studies and studies in long-term follow up, PIs will be asked to identify to MCRF IRB the number of subjects who withdrew from the study, and the reasons for withdrawal.

4. ADDITIONAL RESOURCES

4.1. References:

- FDA Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials
- OHRP Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues

4.2. Supporting documents available:

- None

5. DOCUMENT HISTORY

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1.0	New Document in Document Control system transferred from Policy & Handbook Library - #4560.0 (no changes made)
2.0	
3.0	

6. DOCUMENT PROPERTIES

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