Marshfield Clinic

Unanticipated Problems, Reporting and Review of

1. SCOPE

1.1. System Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. Adverse Event

- Any unfavorable medical occurrence in a human subject, including any sign, symptom, or disease temporally associated with the subject's participation in a research project.

2.2. Investigator-Initiated Research

- Research for which a Marshfield Clinic investigator has overall responsibility for the conduct of the entire research study. The study may be limited to Marshfield Clinic, or it may involve participation by collaborating institutions.

2.3. Minimal Risk

- The probability and magnitude of harm are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

2.4. Multi-Center Research

- Research for which Marshfield Clinic's role is limited to being one of several participating sites, and a Marshfield Clinic investigator is responsible only for the local conduct of the study.

2.5. Unanticipated Problem Involving Greater than Minimal Risk to Subjects or Others

- Based upon OHRP and FDA guidance, any incident, experience, or outcome that falls into one of the following eight categories:
  - ◊ A series of unexpected adverse events that:
    - Upon analysis, the sponsor of multi-center research, or the Principal Investigator (PI) for Marshfield Clinic investigator-initiated research, determines were not isolated occurrences, and are significant to the safety, rights and welfare of subjects; or
    - While described in the investigator's brochure, protocol, or informed consent documents, upon analysis, the sponsor of multi-center research, or the PI for investigator-initiated research, determines are occurring at a greater frequency, or greater severity, than expected.
  - ◊ A single adverse event that represents a serious and unexpected adverse event if there is evidence to suggest a causal relationship between drug and adverse event. Some examples are events that are rare in the absence of drug exposure, such as agranulocytosis, hepatic necrosis, or Stevens-Johnson Syndrome. To be reportable as such, the Sponsor or local PI, in the case of investigator-initiated research, will have evaluated the event and

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provided a determination that it reaches the threshold of an Unanticipated Problem.

◊ A single incident, experience, or outcome that meets all of the following:

Is unexpected or unintentional, given the research procedures described in the IRB-approved research protocol and related documents including the informed consent document, and given the characteristics of the subject population being studied;

Is related, or possibly related, to participation in the research based upon OHRP guidance. "**Possibly related**" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;

Suggests that the research places subjects or others at a greater than minimal risk of harm, including physical, psychological, economic, or social harm, than the risk previously known or recognized; and

◊ Would cause the sponsor of multi-center research or PI for Marshfield Clinic investigator-initiated research to modify the investigator's brochure, protocol, or informed consent document, or would prompt other action to ensure the protection of human subjects.

◊ Complaints from research participants that indicate an unanticipated greater than minimal risk

◊ Interim analysis or publication of results that suggest risk to participants is increased and greater than minimal

◊ any event that requires prompt reporting to the IRB according to the research protocol or the sponsor and involves greater than minimal risk

◊ Breaches of confidentiality that represent a greater than minimal increase in risk to participants

◊ Changes made to the research, without prior IRB approval, in order to eliminate apparent, immediate harm and involve greater than minimal risk

2.6. Unanticipated Problem Involving Not Greater than Minimal Risk to Participants or Others

◊ A single incident, experience, or outcome that meets all of the following:

Is unexpected or unintentional, given the research procedures described in the IRB-approved research protocol and related documents including the informed consent document, and given the characteristics of the subject population being studied; and

Is related, or possibly related, to participation in the research based upon OHRP guidance. "**Possibly related**" means there is a reasonable possibility that the incident, experience, or

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outcome may have been caused by the procedures involved in the research; and

Suggests that the research places subjects or others at increased, but no **greater than minimal** risk of harm, including physical, psychological, economic, or social harm, than the risk previously known or recognized; or

◊ Complaints from research participants that indicate a not greater than minimal unanticipated risk; or

◊ Interim analysis or publication of results that suggest risk to participants is minimally increased; or

◊ any event that requires prompt reporting to the IRB according to the research protocol or the sponsor and involves not greater than minimal risk; or

◊ Breaches of confidentiality that minimally increase risk to participants; or

◊ Changes made to the research, without prior IRB approval, in order to eliminate apparent, immediate harm, and involving not greater than minimal risk

3. PROCEDURE BODY

45 CFR 46.103(b)(5) requires institutions like Marshfield Clinic that have filed Federal-Wide Assurances (FWAs), and engage in human subjects research, to have written procedures for ensuring prompt reporting of Unanticipated Problems to an Institutional Review Board (IRB), appropriate institutional officials, and federal department or agency heads. This procedure outlines federal guidance, and describes reporting and review processes.

3.1. Federal Guidance

a. The message conveyed by both the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP) and the Food and Drug Administration (FDA) is to reduce the number of adverse event reports submitted to IRBs, particularly from multi-center trials. Both agencies have clarified that only adverse events meeting the criteria for an "Unanticipated Problem" should be reported to an IRB for consideration.

b. OHRP

- The document "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risk to Subjects or Others and Adverse Events" (January 15, 2007), explains the definition of Unanticipated Problem. Further, it states:
  - "Investigators and IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials . . . . OHRP advises that it is neither useful or necessary under . . . 45 CFR 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to all investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported . . . when a determination has been made that the events meet the criteria for an Unanticipated Problem. OHRP expects that individual external adverse events rarely will meet the criteria . . . ."

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- OHRP has also addressed IRB considerations of Unanticipated Problems outside the context of multi-center trials. It has stated, "Upon becoming aware of any other incident, experience or outcome (not related to an adverse event) that may represent an Unanticipated Problem, the investigator should assess whether the incident represents an Unanticipated Problem [by applying the definition provided]. . . . If the investigator determines that the incident, experience, or outcome represents an Unanticipated Problem, the investigator must report it promptly to the IRB."
- OHRP has also addressed the IRB's role upon receiving an Unanticipated Problem report: "When reviewing a particular incident, experience, or outcome reported as an Unanticipated Problem by the investigator, the IRB may determine that it does not meet all three criteria for an Unanticipated Problem."

c. FDA

- The FDA rule at 21 CFR 312, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Requirements for Bioavailability and Bioequivalence Studies in Humans" (effective March 2011) explains what adverse events must be reported by sponsors investigating drugs under an IND to the FDA, which in turn, must be reported to participating investigators and IRBs.
  - The rule was revised to include new definitions of "adverse event," "life-threatening adverse event," "serious adverse event," "suspected adverse reaction," and "unexpected adverse event." It explains which individual events must be reported, and which events can be aggregated and compared to a control group.
  - The rule requires investigators to report any serious adverse event to sponsors, and to include "an assessment of whether there is a reasonable possibility that the drug caused the event."
  - The rule also explains when there is a "reasonable possibility" to suggest a causal relationship between the drug and the adverse event. The FDA states that under the previous rule, sponsors frequently reported individual events for which there was little reason to believe that the drug caused the events. Under the current rule, the FDA still states that the most difficult determination is whether a "suspected adverse reaction" must be reported. It confirms that sponsors are to report:

> "[A]ny suspected adverse reaction that is both serious and unexpected . . . only if there is evidence to suggest a causal relationship between the drug and adverse event, such as: (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure . . . (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug . . . (C) An aggregate analysis of specific events observed in a clinical trial . . . that indicates those events occur more frequently l the drug treatment group than in a concurrent or historical control group."

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- The FDA document, "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subjects Protection" (January 16, 2009) also sets forth the expectations for reporting adverse events as Unanticipated Problems. It also supports the recommendations of OHRP:
  - "The requirement that investigators notify IRBs when an 'Unanticipated Problem' occurs is intended to provide IRBs with an alert mechanism when new risks to study subjects come to light. . . . With few exceptions that are rare in the absence of drug exposure, such as agranulocytosis, the FDA believes that an individual adverse event report cannot be readily concluded to represent an Unanticipated Problem, even if the event is not addressed in the investigator's brochure, protocol, or informed consent documents."
  - "Individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an Unanticipated Problem. FDA believes that reports that lack such evaluation should not be provided to the IRB, since the IRB will be unable to assess the significance of the report for the rights and welfare of human subjects in the study."

3.2. Reporting Unanticipated Problems Involving Risk to Subjects or Others to the Marshfield Clinic Research Foundation IRB (MCRF IRB)

a. Investigators must report all Unanticipated Problems Involving Risk to Subjects or Others, per the document "Reporting to IRB, Institutional Officials, and Regulatory Bodies." The Unanticipated Problem should be reported to the IRB regardless of whether it occurs during or after the completion of the study or after subject withdrawal. Reporting also applies to Unanticipated Problems Involving Risk to Subjects or Others that occur at a collaborating institution for whom MCRF is serving as IRB of Record.

- Investigators must use the form, "IRB Unanticipated Problem Involving Risks to Participants of Others Report" and submit it to the Office of Research Integrity & Protections (ORIP) within ten days of any research team member becoming aware of the Unanticipated Problem.
- For Multi-Center Research, sponsors should submit any documentation supporting their Unanticipated Problem determination.

b. IRB Review of Unanticipated Problems involving Risk to Subjects or Others The IRB Chair or designee will review the Unanticipated Problem Involving Risk to Subjects or Others reporting form upon receipt in ORIP and determine whether the Unanticipated Problem Involving Risk to Subjects or Others involves greater or not greater than minimal risk. Those determined by the Chair or designee to not involve greater than minimal risk will be reviewed by the Chair or designee to determine whether additional corrective action is required. If so, requirements will be communicated to the PI in writing. If the information contained in the Unanticipated Problem Involving Risk to Subjects or Others report contains sufficient corrective actions, the Chair or designee will indicate to the PI that , "No further IRB Review Required." Unanticipated Problems Involving Risk to Subjects or Others determined by the Chair or

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designee to involve greater than minimal risk will be scheduled for review at the next available convened IRB meeting.

3.3. Unanticipated Problems Leading to Changes to Protocols or Informed Consent Documents

a. If any Unanticipated Problem prompts changes to the protocol or informed consent documents or processes, investigators must submit to ORIP a, "IRB Change or Update to Original Submission," form concurrently with the IRB Unanticipated Problem Report. See the document, "Changes/Amendments to Approved Research."

3.4. Convened IRB Review of Unanticipated Problems Involving Risk to Subjects or Others

a. ORIP staff will assign two members of MCRF IRB to serve as primary reviewers. Primary reviewers and all other MCRF IRB members will receive the UP reporting form from the sponsor/and or PI, and the IRB approved consent document. The approved protocol is available to all members electronically.

- Primary reviewers are expected to complete a primary reviewer guide. Primary reviewers are also expected to forward any questions or concerns with the study to the ORIP review committee coordinator responsible for the meeting. He or she will coordinate questions and facilitate communication so that, whenever possible, the primary reviewers' questions and the PI's response can be shared and considered at the meeting.
- The members of the IRB may take the following actions in response to the Unanticipated Problem report:

Accept the report with no further action required Require monitoring by the IRB or more frequent IRB review

Require additional steps be added to the corrective action plan

Require notification of participants

Require notification of other organizational entities (e.g. Legal Services, Privacy Officer, Compliance Officer)

Suspend the research

Terminate the research

Other actions as deemed appropriate by the IRB

3.5. Additional Reporting Requirements

a. Federally-Funded Research

- Unanticipated Problems Involving Risk to Subjects or Others that involve greater than minimal risk and occur locally on federally-funded research projects must be promptly reported by the MCRF IRB to OHRP and Marshfield Clinic's Institutional Official (Within ten working days). The PI is responsible for reporting such Unanticipated Problems to ORIP, as well as the DHHS Department or agency head, per the document, "Reporting to IRB, Institutional Officials, and Regulatory Bodies."

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b. FDA Regulated Research

- Unanticipated Problems Involving Risk to Subjects or Others that involve greater than minimal risk and occur locally on Marshfield FDA- regulated research must be promptly reported by the MCRF IRB to the FDA and Marshfield Clinic's Institutional Official (within ten working days), per the document, "Reporting to IRB, Institutional Officials, and Regulatory Bodies."

4. ADDITIONAL RESOURCES

4.1. References:
- None

4.2. Supporting documents available:
- None

5. DOCUMENT HISTORY

Version No.	Revision Description
1.0	New Document in Document Control transferred from Policy and Handbook Library - #2977.7 (no changes made)
2.0	Add hyperlinks to document. Sect. 3.3 Update name of Change or Update Form.
3.0	

6. DOCUMENT PROPERTIES

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