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Reportable New Information – Protocol Deviations

A Spectrum Health IRB Guidance Document

Purpose

This document provides guidance on what deviations to report on the Reportable New Information xForm

Regulatory Guidance

- **45 CFR 46.108(a)(3)(iii)**
- **45 CFR 46.108(a)(4)(i)**
- **45 CFR 46.108(a)(4)(ii)**
- **21 CFR 812.150(a)(4)**

Protocol Deviation Policy Guidance

A protocol deviation occurs when the study departs from the IRB-approved protocol in <u>any</u> way **without the investigator first obtaining IRB approval**.

Federal regulations require the IRB to review and approve all proposed changes to research studies before initiation of these changes, except when changes are "necessary to eliminate apparent immediate hazards to the subject" [45 CFR 46.108(a)(3)(iii)]. Any changes that are made to eliminate apparent immediate hazards to a subject should be reported as soon as possible after they occur (within 5 days) as Reportable New Information item. A Modification submission may also be required if the changes will be incorporated into study procedures and documents.

In addition, the IRB requires prompt reporting of allegations or findings of noncompliance with regulations or noncompliance with the IRB's own requirements and determinations [45 CFR 46.108(a)(i) and 45 CFR 46.108(a)(ii)]. Deviations from the approved protocol, i.e., changes made without prior IRB approval, fall into this category of noncompliance. Deviations must be reported to the IRB with a description of the effect of the deviation on subject safety and a description of how similar events will be

avoided in the future. Once reported, the IRB can make a decision regarding an appropriate response or remedial action. Remedial actions may involve excluding data that was obtained inappropriately or a recommendation for additional monitoring of study procedures.

Deviations range in seriousness according to how the changes may impact subject safety, the degree of noncompliance with federal and state regulations, and the degree of foreknowledge of the event. Anticipated changes to a protocol should always be reported before the event occurrence unless an immediate change is necessary to protect subject safety. Note that repeated deviations of the same type may be an indication that an amendment is needed to permanently change study criteria.

A. Accidental or unintentional protocol deviations that involve risks.

Accidental or unintentional protocol deviations that involved risks must be reported to the IRB according to the SH Policy – "Reportable New Information to the IRB for Previously Approved Research." A **major deviation** is one that may impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study. Major deviations should be reported **within 5 days** of the investigator's knowledge of the deviation.

Examples of emergency protocol deviations:

- Immediate reduction in the study drug dose due to new safety information or serious side effects
- Closure of a study arm due to lack of efficacy

Examples of Major Deviations:

- Failure to obtain informed consent (including lack of appropriate documentation of informed consent)
- Informed consent obtained after subject has already started study procedures
- Use of outdated or otherwise unapproved consent form
- Enrollment of a subject from a federally-defined "vulnerable population," i.e. children, prisoners, pregnant women and fetuses, without prior approval for that vulnerable population group
- Enrollment of subjects before IRB approval of study or after IRB approval of study has expired
- Performing and/or collecting data on additional procedures not approved by the IRB as part of a study
- Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
- Drug dispensing or dosing error
- Use of concurrent medication not allowed on study
- Failure to follow data safety monitoring plan

B. Accidental or unintentional protocol deviations that involve <u>no</u> risks.

If the deviation is a one-time deviation from the IRB-approved protocol and it involved no risks, it should be reported to the IRB at the time of continuing review. A **minor deviation** is one that does **not** impact subject safety, compromise the integrity of the study data, or affect subjects' willingness to participate in the study. Minor deviations should be summarized at the time of continuing review on the Protocol Deviation Tracking Log.

Examples of Minor Deviations:

- Failure to follow the approved study procedure (only considered "minor" if, in the opinion of the PI, the deviation did not affect subject safety or data integrity), for example:
    - study procedure conducted out of sequence
    - failure to perform a required lab test and this lab test is not known to be adversely affected by the study intervention
- Failure of subject to return unused study drug
- Over-enrollment (depending on the nature of the study)
- a participant is seen outside of the visit "window"

What are the protocol deviation reporting requirements for commercially sponsored research?

Sponsored research agreements may require the PI to notify the sponsor of all unplanned deviations or departures from IRB approved protocol procedures. Sponsor reporting requirements for deviations may differ from Spectrum Health IRB reporting requirements. Before a PI signs a research agreement, it is essential for him/her to be aware of those contract terms.

Does the FDA Good Clinical Practice (GCP) Guidance affect reporting of deviations?

Many sponsors require investigators to follow Good Clinical Practice (GCP) guidelines. The GCP Guidance for Industry states:

> "The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB…of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))." (4.5.2 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf)

It is important to understand that the IRB embraces the GCP Guidance, and we are only defining the reporting timeline.