OFFICE FOR EDUCATION & QUALITY IN CLINICAL RESEARCH		
	CATEGORY	**Clinical Research: HSRC**
	SUBJECT	**Adverse Events/Unanticipated Problems Involving Risks to Subjects or Others/Protocol Deviations**
	SOP #	**3.2**
	EFFECTIVE DATE	**August 6, 2008**
	REVISION DATE	**October 17, 2017**

OBJECTIVE

Describe the responsibilities of the research team in reporting unanticipated problems involving risks to subjects or others and/or protocol deviations to the Human Subjects Research Committee. These procedures apply to all clinical research activities approved by the Office for Human Subjects Research conducted within the Hennepin County Medical Center campus.

APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46	Protection of Human Subjects
21 CFR 56	Institutional Review Boards
21 CFR 312	Investigational New Drug Application
21 CFR 812	Investigational Device Exemptions
FDA Information Sheet	Continuing Review after Study Approval

REFERENCES TO RELATED SOPs

SOP 2.1
SOP 2.2
SOP 2.11
SOP 2.12

ATTACHMENTS

Definitions
Unanticipated Problems Involving Risks to Subjects or Others
Sample Adverse Event Tracking Log
Sample Protocol Violation Tracking Log

1) The Principal Investigator must ensure that all research team members are aware of their responsibility to note and report to the Human Subjects Research Committee, and Sponsor as applicable, unanticipated problems involving risks to subjects or others, protocol violations, and incidents of unexpected serious harm (see schematic of unanticipated problems below).

2) Assess subjects at each visit or intervention for unanticipated problems involving risks to subjects or others, incidents of unexpected serious harm, and protocol violations that may have occurred since the previous visit. Information may be elicited from, but not limited to:
   a) Conversations or reports by the subject
   b) Direct observations by research staff (i.e., abnormal vital signs, laboratory results)
   c) Reports by medical care providers
   d) Medical progress reports or interviews
   e) Reports from friends or family
   f) Report of subject's death

2) Manage, treat, and follow the subject as appropriate to the situation using therapeutic interventions, support measures, and reporting parameters outlined in the protocol.

a) The PI will decide if an event or problem is related to the investigational product, most likely related to the investigational product, possibly related to the investigational product, unlikely to be related to the investigational product, or has no relationship to the investigational product.

3) Treatments and treatment outcome must be recorded in the subject's medical records or primary study source documents.

4) Complete the appropriate case report forms**.**

5) If necessary for the immediate care of the subject, the PI is the only member of the research team who may make the decision to break the blind (after consultation with the sponsor if possible). Guiding principle should be the welfare of the subject.
   a) If knowing what substance has been administered will help manage an event or problem, breaking the blind should be considered**.**
   b) If an event or problem can be treated symptomatically, not breaking the blind should be considered.
   c) If the blind is broken, notify the sponsor immediately.

6) All incidents of unexpected serious harm reasonably believed to be research related must be reported promptly to the OHSR (no longer than within 5 working days of knowledge of the incident).

7) All unanticipated problems involving risks to subjects or others reasonably believed to be research related must be reported promptly (no longer than within 5 working days of knowledge of the incident) to the OHSR when the risk is greater than minimal risk to subjects or others. (See definitions and reporting requirements below).

8) Sponsor reporting requirements will be outlined in the protocol.

9) Provide as much information as available with follow-up as more information becomes obtainable.

10) Required information includes, but is not limited to:
   a) Protocol name and number
   b) Subject study identification
   c) Nature of the event
   d) Severity of the event
   e) Probable relationship to the investigational product
   f) Date of the event
   g) Date of resolution if applicable
   h) Results of any laboratory and/or diagnostic testing
   i) The start and stop time and dates of the investigational product administration
   j) A follow-up plan
   k) Outcome of the event

11) Obtain external provider records concerning an incident of unexpected serious harm or unanticipated problem involving risks to subjects or others from outside sources (i.e., private medical provider, secondary hospital), these become source documents.

12) For unanticipated problems when the risk is NOT greater than minimal risk to subjects or others, the report of the unanticipated problem should be included on the next Continuing Review Report or Annual Re-approval Continuing Review Report. See definitions and reporting requirements below.

13) Submit external adverse events (happening at another research institution) which are unanticipated problems involving risks to subjects or others promptly to the HSRC no longer than within 5 days of receipt. (See definitions and reporting requirements below).

14) Protocol deviations should be reported to the OHSR no longer than within 5 days of when they became apparent if risk is greater than minimal risk. Protocol deviations that are minimal risk should be reported on the Annual Reapproval Form. A protocol deviation may consist of, but not be limited to:
    a) Not fully explaining the research study to the subject or neglecting to respond to subjects' questions or concerns
    b) Failing to assure the safety of the research subject by not disclosing risks or discomforts nor providing information regarding new significant findings during the study, or by failing to treat, document, and report adverse events as required
    c) Not assuring the integrity of the research data by having data incorrectly collected or data that is missing or left out

15) Keep all correspondence to and from the HSRC and the sponsor in the regulatory binder.

1) Definitions

a) Unanticipated problem involving risks to subjects or others – a problem that:
   i) Is unanticipated or unexpected
   ii) Involves risks to subjects or others; and
   iii) Is reasonably believed to be related to research participation

b) Unexpected serious harm is a serious adverse event(s) that is/are not anticipated but is/are reasonably believed to be protocol related.

c) Adverse event- any untoward medical occurrence in a subject receiving a test article and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the test article, whether or not related to the product.

d) Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research 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. This definition shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

2) Reporting Requirements

a) The following unanticipated problems are required to be reported by investigators and/or research support personnel:
   i) Internal adverse events which are unexpected and reasonably believed to be related to the research
   ii) External adverse events which are unanticipated problems involving risks to subjects or others
   iii) Other unanticipated information that indicates subjects or others might be at increased risk of harm including:
      (1) Any event that requires prompt reporting according to the protocol or sponsor
      (2) Any accidental or unintentional change to the HSRC approved protocol that involved risks or has the potential to recur
      (3) Any change to the protocol taken without prior HSRC review to eliminate apparent immediate hazard to a research subject
      (4) Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research
      (5) Any complaint of a subject that indicates an unanticipated risk or which cannot be resolved by the research staff
      (6) Any other event that would be considered an unanticipated problem involving risk to subjects or others

b) The unanticipated problems (as outlined in #3) should be reported to the OHSR regardless of whether they occur during the study, after study completion, or after subject withdrawal or completion.
   i) For unanticipated problems when the risk is not greater than minimal risk to subjects or others, the report of the unanticipated problem should be included on the next Continuing Review Report or Annual Re-approval Continuing Review Report
   ii) For unanticipated problems when the risk is greater than minimal risk to subjects or others, the report of the unanticipated problem should be reported within 5 days to the OHSR.
   iii) All instances of unexpected serious harm should be reported to the OHSR within 5 days.

REVIEW: UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS

Unanticipated problem involving risks to subjects or others is a problem that:

1. is unanticipated or unexpected;
2. involves risks to subjects or others; and
3. is reasonably believed to be related to research participation

Is this an unanticipated problem involving risks to subjects or others?

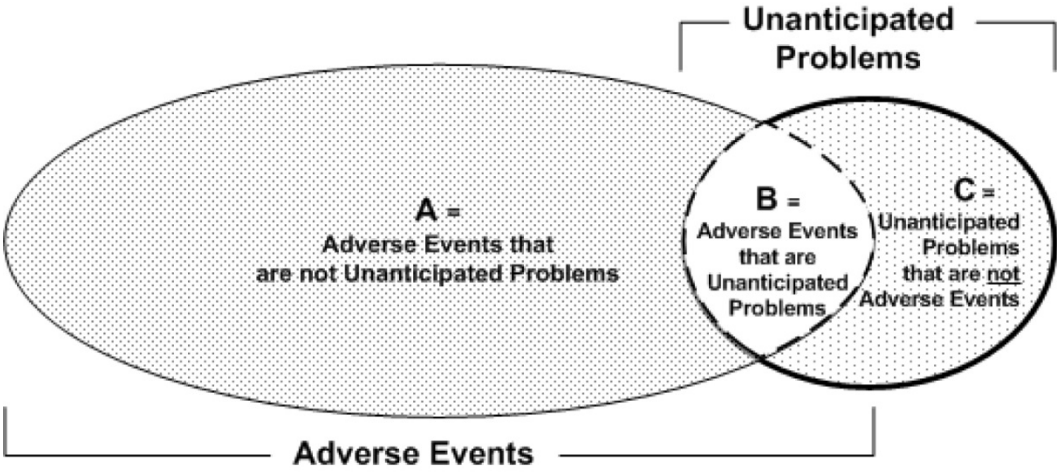
_____ NO _____ YES

If yes, is additional information needed and if so, what information?

If yes, does it reasonably appear that study subjects are at increased risk if the protocol were to continue? _____ NO _____ YES

If yes, possible actions include:

- suspend approval of the research pending further investigation;
- refer the matter to the Chair; and/or
- refer the matter to the HSRC for discussion and further action



Under applicable regulations: Do not report A, Do report (B+C)

SAMPLE EVENT/UNANTICIPATED PROBLEM TRACKING LOG

PI

HSRC #

Study Title

Sponsor

Subject ID	Start Date	Resolved Date	Event Description/Unanticipated problem	Severity	Relationship to Investigational Product	Date Sent to HSRC	Date Sent to Sponsor	Date of HSRC Response

SAMPLE PROTOCOL DEVIATION TRACKING LOG

PI

HSRC #

Study Title

Sponsor

Subject ID	Deviation Date	Description	Date Sent to HSRC	Date Sent to Sponsor	Date of HSRC Response	Date of Sponsor Response