IU Kokomo Standard Operating Procedures (SOPs) for
UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS AND NONCOMPLIANCE
Approved 7/20/05

1. INTRODUCTION

All members of the IU Kokomo research community involved in human subjects research are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and institutional policies governing the conduct of research involving human subjects.

Federal regulations 45 CFR 46.103 and 21 CFR 56.108 require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB, and any suspension or termination of IRB approval. The IU Kokomo IRB will review allegations and reports of unanticipated problems involving risks to subject or others and noncompliance and fulfill reporting requirements to the appropriate institutional officials, federal departments or agencies, and appropriate other entities.

2. OBJECTIVES

The objectives of this SOP are to:

2.1. Outline the procedures to ensure prompt reporting of unanticipated problems involving risks to subjects or others, noncompliance, and suspensions or terminations of IRB approval;

2.2. Explain the IRB's potential actions in response to allegations and reports of unanticipated problems involving risks to subjects or others and noncompliance.

3. SCOPE

These policies and procedures apply to all research activities of faculty, staff, student, or others who are involved in human subjects research that fall under the jurisdiction of the IU Kokomo IRB.

4. RELEVENT DEFINITIONS

4.1. **Administrative Noncompliance**: Noncompliance related to incomplete submission of IRB forms or related documents.

4.2. **Allegation:** An assertion made by a second party that must be proved or supported with evidence to either confirm or deny.

4.3. **Continuing Noncompliance**: Repeated noncompliance that, in the opinion of the IRB, Chair, or Chair's designee, suggests the likelihood that noncompliance will continue without intervention.

4.4. **List of Events that Require Prompt Reporting to the IRB:** Any of the following:

4.4.1 Event (including adverse events, injuries, side effects during the research study), which in the opinion of the principal investigator (PI)

4.4.1.1 caused harm to one or more subjects or others, or placed one or more subjects or others at increased risk of harm;
4.4.1.2 was unexpected; AND
4.4.1.3 was related to the research procedures

Note: After the study is closed with the IRB, these events should only be reported if they are profound or they demonstrate long-term risks that would necessitate notifying subjects.

4.4.2 Protocol deviation/violation (as defined under this policy and on-site only)

4.4.3 Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject (on-site only)

4.4.4 Interim findings and safety monitoring report that indicate an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency

4.4.5 Publication in the literature that indicates an unexpected change to the risks or potential benefits of the research

4.4.6 Complaint of a subject that indicates unexpected risks, or complaint that cannot be resolved by the research team (on-site only)

4.4.7 Noncompliance (as defined in this policy)

4.5. **Minor Noncompliance:** Noncompliance that is not administrative, serious, or continuing.

4.6. **Noncompliance:** Failure to comply with any of the federal or state regulations or institutional policies governing human subjects research or the requirements or determinations of the IRB.

4.7. **On-Site**: Related to a subject enrolled in an IU Kokomo IRB-approved research study.

4.8. **Off-Site**: Related to a subject enrolled in an external research study.

4.9. **Protocol Deviation/Violation:** An accidental or unintentional change to the IRB-approved protocol that placed one or more subjects at increased risk, or has the potential to occur again.

4.10. **Related to the Research Procedures**: If in the opinion of the PI, an event was more likely than not to be caused by the research procedures.

4.11. **Report:** An occurrence of noncompliance or unanticipated problems involving risks to subjects or others that does not require further information to confirm.

4.12. **Serious Noncompliance**: Failure to comply with any of the federal or state regulations or institutional policies governing human subjects research that, in the judgment of the IRB, Chair, or Chair's designee, increases the risks to subjects, decreases potential benefits to subjects, or compromises the integrity of the human research protection program. An example of serious noncompliance includes conducting human subjects research without appropriate IRB approval.

4.13. **Suspension**: Temporary cessation of some or all activities in a currently approved research study.

4.14. **Termination**: For purposes of this SOP, this term refers to a determination made by the IRB to permanently withdraw approval for some or all activities of a currently approved research study.

4.15. **Unanticipated:** Any untoward event that is unforeseen, caused serious harm or places a person at increased risk of serious harm, and is related to the research procedures. "Unanticipated" is not synonymous with "unexpected." A research protocol can monitor for an "unexpected" event, but cannot monitor for an unforeseen, or "unanticipated," event. All "unanticipated" events are "unexpected," but not *vice versa*.

4.16. **Unanticipated Problem Involving Risk to Subjects or Others:** Any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, **and** (3) is related to the research procedures.

4.17. **Unexpected:** When the specificity or severity of an event is not accurately reflected in the informed consent document.

5. POLICY AND ASSOCIATED PROCEDURES

5.1. Due to possible conflicts in scheduling or conflicts of interest there will be times when the IRB Chair will need to name a designee to act in his or her stead. Henceforth in this document IRB Chair will mean the IRB Chair or the designee.

5.2. The IRB has authority to and will investigate (or appoint some individual or entity to investigate) all credible allegations or reports of unanticipated problems involving risks to subjects or others or noncompliance. The level of investigation will depend on the seriousness of the situation and the potential risk to subjects.

5.3. Allegations or reports of unanticipated problems involving risks to subjects or others or noncompliance can come from a number of different sources, including investigators, members of the research team, study sponsor, regulatory body (e.g. OHRP, FDA), subjects and/or their families, institutional personnel or committees, the media, the public, or anonymous sources. Additionally, the IRB can identify noncompliance during its review of research studies.

5.4. Principal investigators (PI) must report to the IRB as soon as possible, but in all cases within 3 working days (for on-site events) or 10 working days (for off-site events) any event that appears on the **List of Events that Require Prompt Reporting to the IRB.** All events other than noncompliance should be reported on the **IU Kokomo Reporting Form for Events that Require Prompt Reporting to the IRB**. Noncompliance should be reported via a memo or other appropriate means.

5.5. Investigators are not required to report events other than those on the **List of Events that Require Prompt Reporting to the IRB**. However, the IRB office will accept reports of other events when sponsors require investigators to report such events to the IRB, or when the investigator is unsure whether the event should be reported. See Appendix A for the procedure for processing these reports.

5.6. **Handling Event Reports**

5.6.1 When the IRB office receives an event report, the staff will ensure the report contains complete information. If, in the opinion of the IRB Chair, the form is incomplete or answers appear unsatisfactory, the Chair may:

5.6.1.1 Return the report to the PI to request additional information. A copy of the report is kept with the IRB records until the original report is returned. In the case of unanticipated problems involving risks to subjects or others, if the IRB Chair determines that the event does not meet the reporting requirements, the report will be returned to the PI indicating such determination.

5.6.1.2 Contact the PI (or designated contact person) via telephone or e-mail to obtain additional information. If the contact is made via telephone, the IRB Chair will document corrections or additions to the report, indicating the date. The IRB Chair will inform the PI (or designated contact person) to document these corrections or additions in his/her records. If the contact is made via e-mail, the IRB Chair will attach the PI's (or designated contact person's) response to the report.

5.6.2 If, in the opinion of the IRB Chair, the event is noncompliance that is clearly administrative in nature, he or she will take steps to resolve the issue, conferring with the IU Kokomo IRB if necessary.

5.6.3 If, however, the IRB Chair believes the event to be minor noncompliance or clearly not an unanticipated problem involving risks to subjects or others, the information will be reviewed through the expedited review procedure.

5.6.3.1 The IRB Chair may request additional information, as needed, in order to make an informed decision about whether the event is considered an unanticipated problem involving risks to subjects or others or regarding the degree of noncompliance and appropriateness of the proposed action plan.

5.6.3.2 If, after review of the report, the IRB Chair determines the event either (1) is NOT an unanticipated problem involving risks to subjects or others and the event has been appropriately resolved; or (2) is minor noncompliance with an adequate corrective action plan, he/she will indicate this by signing the report, which will be attached to the study file or the investigator's general file. The report will then be reported to the full IRB at its next convened meeting. If, however, the IRB Chair determines that the event requires additional resolution or that the corrective action plan is not adequate, the IRB Chair may request additional information from the investigator.

5.6.3.3 If, after review of the report, the IRB Chair believes it to be an unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, or the event cannot be adequately resolved, the report will be forwarded to the full IRB for review and handled according to the unanticipated problems involving risks to subjects or others procedures.

5.6.4 If, in the opinion of the IRB Chair, the event report may represent an unanticipated problem involving risks to subjects or others or may be serious or continuing noncompliance, the report will be sent to the full IRB for review and determination on the matter. Procedures for unanticipated problems involving risks to subjects or others will then be followed.

5.6.5 If, in the opinion of the IRB Chair, the event requires immediate action before receipt of a completed report, the information will be referred to the IU Kokomo IRB.

5.7. **Handling Allegations of Unanticipated Problems Involving Risks to Subjects or Others or Noncompliance**

5.7.1 When the IRB Chair receives an allegation of either an unanticipated problem involving risks to subjects or others or of noncompliance, the Chair must immediately report it to the IU Kokomo IRB.

5.7.2 The IRB Chair will compile information regarding the allegation and present it to the IU Kokomo IRB .

5.7.3 The IU Kokomo IRB will determine if additional information gathering is necessary and if so, will direct the IRB Chair on how to proceed. For example, they may request that additional information be obtained from any or all of the following: complainant, respondent, or the investigator, as well as any other individuals or entities as deemed necessary.

5.7.4 If, in the opinion of the IRB Chair, the alleged noncompliance or unanticipated problem involving risks to subjects or others is minor or without merit, the IRB Chair will document the findings and outcome of the discussions in writing. The IU Kokomo IRB Chair will communicate this documentation to the complainant, respondent, and investigator, as appropriate, and report it to the IRB at its next regularly scheduled meeting. Additionally, it will be placed in the appropriate study file or general file of the investigator.

5.7.4.1 Administrative noncompliance will be further handled as in **Handling Event Reports** 5.4.2.

5.7.4.2 Minor noncompliance or events that clearly do not represent unanticipated problems involving risks to subjects or others will be further handled as in **Handling Event Reports** 5.4.3.

5.7.5 If the initial fact-finding does not result in resolution of the allegation or if the IRB Chair determines the allegation could represent unanticipated problems involving risks to subjects or others or to be serious or continuing noncompliance, the matter will be referred to the full IRB for review and appropriate action. If the full IRB determines the allegation to NOT represent an unanticipated problem involving risks to subjects or others or to be minor noncompliance, the IRB Chair will prepare a report (typically this report is the summary that appears in the meeting minutes) that details the nature of the allegation and event, the findings and any actions taken or recommendations made by the IRB. This information will be forwarded to the PI.

5.8. If, at any point during the process, the IRB Chair believes the allegation raises issues of legal liability or there is a threat or perceived threat of a lawsuit, IU's University Counsel office will be contacted.

5.9. If, in the opinion of the IRB Chair, the allegation is considered to represent an unanticipated problem involving risks to subjects or others or to be serious or continuing noncompliance, the allegation will be sent to the full IRB for review.

5.10. **IRB Actions Regarding Unanticipated Problems Involving Risks to Subjects or Others or Serious or Continuing Noncompliance**

5.10.1 When the IRB determines that allegations or reports are either serious or continuing noncompliance or represent unanticipated problems involving risks to subjects or others, it will determine the appropriate action that must be taken. Any action taken or sanction imposed will consider the rights and welfare of subjects. Possible actions or sanctions include, but are not limited to:

5.10.1.1 Dismissal of the allegation or report as unjustified – no action.
5.10.1.2 Approve the investigator's proposal for correction – no further action.
5.10.1.3 Request additional information to determine if a change in risk/benefit has occurred pending final action.
5.10.1.4 Notify and/or involve other individuals from the University (e.g. Dean, supervisor).
5.10.1.5 Restrict use of research data for publication.
5.10.1.6 Appoint a subcommittee to investigate and assess the event.
5.10.1.7 Request an audit be conducted on the study that is the subject of the allegation or report.
5.10.1.8 Require modification to the research protocol and/or informed consent document.
5.10.1.9 Require past and/or current subjects to be informed of the event and/or to be reconsented if the information may relate to their willingness to continue to take part in the study.
5.10.1.10 Require withdraw of currently enrolled subjects if it is determined to be in their best interest.
5.10.1.11 Require remediation, mentoring, or educational measures.
5.10.1.12 Modify the continuing review cycle.
5.10.1.13 Require increased reporting by the investigator and/or increased monitoring of the research and/or informed consent process.
5.10.1.14 Restrict investigator's human research activities, including suspension or limiting the privilege to minimal risk or supervised projects.
5.10.1.15 Suspend approval of or terminate one, more, or all of the investigator's studies or suspend specific research activities (e.g. recruitment, enrollment, interaction/intervention, and/or follow-up) following the procedures in **5.11 Suspensions and Terminations Due to Unanticipated Problems Involving Risks to Subjects or Others and Noncompliance**.

5.10.1.16 Consult with the IRB.

5.10.1.17 Refer the issue to other University officials or committees for possible further review and action.

5.10.2 When the IRB determines that allegations or reports are either serious or continuing noncompliance or represent unanticipated problems involving risks to subjects or others, it will be reported in accordance with the **Reporting SOP**.

5.11. **Suspensions and Terminations Due to Unanticipated Problems Involving Risks to Subjects or Others and Noncompliance**

5.11.1 The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the institutional policies, is not in compliance with federal or state regulations, or has been associated with unexpected serious harm to subjects.

5.11.2 Suspensions and terminations cannot be overturned by Institutional Officials.

5.11.3 Suspensions may be made on an urgent basis by either the IRB Chair or the full IRB; however, they can only be lifted by the full IRB. Anytime an IRB Chair suspends research, the full IRB will be notified and the matter reviewed. Terminations due to noncompliance can only be made by the full IRB.

5.11.4 When the IRB suspends or terminates a research study, it will consider whether the suspension or termination requires that subjects be withdrawn from the study and/or places them at risk of harm.

5.11.5 When subjects must be withdrawn from a study, the IRB will consider and determine necessary termination procedures for the safety, rights, and welfare of those subjects.

5.11.6 If the IRB determines that the suspension or termination will place subjects at risk of harm and/or follow-up of subjects for safety reasons is permitted or required, the IRB will determine what subjects are to be told and the manner in which they are to be notified, e.g. in writing or by telephone. Depending upon the reasons for the suspension or termination and the design of the study, the IRB may require that any the following subjects be notified of the suspension or termination:

5.11.6.1 All subjects who have been or who are enrolled;

5.11.6.2 Only subjects who are currently enrolled and on protocol; or

5.11.6.3 Only subjects who participated in a certain aspect of the study.

5.11.7 **VA Research**. Suspensions to research conducted at or funded by the VA require that the investigator submit to the IRB Chair a list of subjects for whom the suspension would cause harm. The IRB Chair will consult with the VA Chief of Staff to determine whether the subjects could continue.

5.11.8 The PI may make a request to attend an IRB meeting to discuss a suspension or termination in order to provide clarification of the issues and/or may request in writing that the IRB reconsider the suspension or termination, within 10 days of such action.

5.11.9 When the IRB chair or convened IRB suspends or terminates approved research, it will be reported in accordance with the **Reporting SOP**.

6. APPLICABLE REGULATIONS AND GUIDELINES

6.1. 45 CFR 46.103(b) Protection of Human Subjects
(http://a257.g.akamaitech.net/7/257/2422/05dec20031700/edocket.access.gpo.gov/cfr_2003/octqtr/45cfr46.103.htm)

6.2. 45 CFR 46.113, Suspension or Termination of IRB Approval of Research
(http://a257.g.akamaitech.net/7/257/2422/05dec20031700/edocket.access.gpo.gov/cfr_2003/octqtr/45cfr46.113.htm)

6.3. 21 CFR 56.108 IRB Functions and Operations
(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=56.108)

7. RESOURCES AND REFERENCES

7.1. IUPUI/Clarian SOP for Reporting

Review of Non-Reportable Events

1. Per IRB policy, investigators are required to submit **ONLY** those events that are (1) serious; (2) unexpected; **AND** (3) related to the research procedures. IND safety reports that do not meet the three criteria do not require submission to the IRB. However, the reports should be reviewed and dated by the investigator and filed with research documents. If required by the sponsor, you may notify the IU Kokomo IRB Chair of these events using the form in Appendix B.

2. Investigators are to submit (2) copies of the **Tracking Log for Non Reportable Events** (hereafter referred as **Form**). Upon receipt of the Form, IU Kokomo IRB office staff will check the form for completeness.

3. If any applicable sections of the **Form** are incomplete or have been answered unsatisfactorily:

    a. IU Kokomo IRB office staff may return the **Form** and any attachments to the investigator with an explanation and required date of response. A copy of the **Form** is kept with the IU Kokomo IRB office records until the original is returned.
    b. IU Kokomo IRB office staff may contact the investigator or designated contact directly to obtain additional information or clarification. Corrections or revisions are documented in the IU Kokomo IRB office file, indicating the date, the person spoken with, and the IRB staff making the correction or revision. IRB office staff will request the corrections or revisions also be made to the investigator's records.
    c. If, in the opinion of the IRB office staff, the event requires immediate action before receipt of a completed **Form**, the information will be referred to the IRB Chair.

4. If the investigator indicates that any event was (1) serious; (2) unexpected; AND (3) related to the research procedures, the IRB Chair will contact the investigator to request that the investigator complete the **Unanticipated Problems Involving Risks to Subjects or Others Reporting Form**. This report will then be handled as in **5.5 Handling Event Reports**. IRB office staff will track this request.

5. Otherwise, IRB office staff will stamp the **Form** acknowledging receipt by the IRB office, sign and date the **Form**, and return a copy of the **Form** to the investigator.

6. If the investigator indicates that the consent document or protocol should be revised, IRB office staff will process these requests according to procedures for processing amendments.

Appendix B

Tracking Log for Non Reportable Events

Per IRB Office policy, Investigators are required to submit **ONLY** those events that are 1) Serious, 2) Unexpected **AND** 3) likely related to the research procedures. IND safety reports that do not meet the three criteria do not require submission to the IRB Office. However, the reports should be reviewed and dated by the Principal Investigator and filed with research documents. If required by the sponsor, you may notify the IRB Office of these events with this form.

Principal Investigator:	**Study Contact:**
IRB Study Number:	**Phone Number:**
Study Title:	

Mfr. Control # Or Reference No.	Report Type Initial or Follow-up (I / F #)	Name of Event	In the opinion of the principal investigator:			Is a change to the consent document or protocol recommended? Yes/No *(If Yes, attach an amendment request)*	Reports received w/o PI initials/date will be returned without review. PI Initials and Date of Review
			Was the event unanticipated and/or unforeseen? Yes/No	Was the event's specificity and severity inconsistent with the informed consent document Yes/No	Was the event related to the study and/or research activity? Yes/No		
			If the answers to the above three questions are all yes, you must report this event within 3 days using an UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS REPORTING FORM.				
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	
			☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	☐Yes ☐ No	

For IRB Office use only

IRB Office Staff Signature ______________________ Date ______________ Acknowledgement Stamp