

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32



Campus Institutional Review Board
University of Missouri-Columbia


Unanticipated Problems or Adverse Events
Involving Risks to Participants and Others

Policy Number 2876.32

Reviewed by: Michele Reznicek, Campus IRB Compliance Officer
Reviewed by: Janelle Greening, Quality Assurance Associate
Reviewed by: Campus IRB Membership


Effective Date: December 12, 2007

Approval Authority:


Signed _____
IRB Chair

Date December 12, 2007

Institutional Approval:


Signed _____
Associate Vice-Chancellor for Research

Date December 12, 2007

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

1.0 Policy

The Campus Institutional Review Board (Campus IRB) has established policies and procedures for ensuring prompt reporting to the IRB and appropriate institutional officials regarding unanticipated problems or adverse events involving risks to subjects or others in accordance with State, Federal and local law.

2.0 Scope

The Campus IRB review process provides for a comprehensive practical approach to reporting unanticipated problems or events involving risks to subjects or serious adverse events regarding any human subject research project, based upon the reasonable interpretation and application of the federal regulations.

3.0 Purpose

The purpose of this policy is to outline the procedure to ensure prompt reporting to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency heads of unanticipated problems involving risks to participants or others.

The Campus IRB requires the prompt reporting of any serious adverse events that result as a result of participation in the research, involving risks to the subject or others. This policy establishes the reporting requirement and types of adverse events and unanticipated problems that an investigator must promptly report to the Campus IRB.

4.0 Standard Operating Procedure

DEFINITIONS:

Adverse Event: A harmful or unfavorable outcome occurring to a human subject as a result of participation in a research study that is both (1) unexpected; and (2) related to the research.

Others: Individuals who are not research subjects.

Related: An event that is more than likely associated or caused by the research procedures.

Risks: The occurrence of harm or probability that harm might occur. The harm may be physical, psychological, financial, social, economic, or legal.

Serious: An event that resulted in or required intervention to prevent death, a life threatening event, injury, hospitalization, prolongation of hospitalization, emergency visit, a persistent or significant/incapacity, medical treatment, or a congenital anomaly/birth defect. An event may be serious if it results in grave or severe harm to a subject or others.

Unanticipated Problem or Event: Any information, event, or activity that at the time of its occurrence, is either (1) unexpected; or (2) unforeseeable based on the information that was proposed or previously provided to the IRB.

Unanticipated problems involving risks to participants or others: Any event that (1) was unforeseen and (2) indicates that the research procedures increased the risk to participants or others.

A. Campus IRB Receipt of Notice

The Campus IRB is required to investigate any assertions that an unanticipated problem or adverse event has occurred. Upon receipt of notice of such an event, the Campus IRB will immediately confirm the following:

1. The Principal Investigator has assured the safety and welfare of the human subject participants;
2. The investigator(s) possess the professional qualifications and experience to adequately meet the degree of proposal complexity and risk to human subjects to continue to conduct and oversee the project;
3. Immediately initiate an investigation into the problem or event;
4. Request that the Principal Investigator complete and submit an electronic “Unanticipated Problem or Adverse Event” Report within 5 business days of the event;
5. Request any supplemental information as needed.
6. Proceed with the investigation through the Campus IRB Review Process provided below.

I. THE PROCESS FOR DETERMINING WHETHER THERE IS AN UNANTICIPATED PROBLEM INVOLVING RISKS TO PARTICIPANTS OR OTHERS

The Campus IRB shall review ALL Unanticipated Problem or Adverse Event Reports to assess the level of risk to the subjects and others. The event is unexpected given the research procedures proposed and approved by the IRB and the characteristics of the subject population being studied.

CAMPUS IRB APPROACH:

- A. **Step 1. INVESTIGATOR RESPONSIBILITY:** Notice to Campus IRB of unanticipated problem involving risks to participants or others.

REPORTING REQUIREMENTS:

1. The investigator is required to notify the Campus IRB within 5 days of all events that might represent unanticipated problems or events involving risks to participants or others in accordance with the “Investigator or Key Personnel Responsibilities” policies.
2. **OFFSITE ACTIVITIES:** The investigator is required to report all events that might represent unanticipated problems or events involving risks to participants or others in accordance with the “Investigator or Key Personnel Responsibilities” policies within 5 days from notification of occurrence.
3. **DEATH:** The investigator is required to notify the Campus IRB within 24 hours if a death occurs. The investigator must comply with the “Investigator or Key Personnel Responsibilities” policies.
4. **MODE OF REPORTING:** The investigator is required to report events that might represent unanticipated problems involving risks to participants or others via the eIRB electronic submission of the “Campus IRB Unanticipated Problems or Adverse Event Report” form.

5. ASSESSMENT OF WHETHER THE ACTIVITY IS AN UNANTICIPATED PROBLEMS INVOLVING RISKS TO PARTICIPANTS OR OTHERS
 - The activity must be “unexpected” (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
 - Suggests the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
6. PROBLEMS THAT INVESTIGATORS MUST PROMPTLY REPORT TO THE CAMPUS IRB:
 - a. An adverse event occurs when in the opinion of the principal investigator is both unexpected and related. Adverse events not meeting these criteria would not be considered unanticipated problems.
 - An adverse event is “unexpected” when its specificity and severity are not accurately reflected in the research materials (e.g., informed consent document, protocol, etc.).
 - An adverse event is “related to the research procedures” if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants.
 - b. Information that indicates a change to the risks or potential benefits of the research.
 - c. Incarceration of a participant in a protocol not previously approved to enroll prisoners.
 - d. Study suspension that may increase risk to participants needing treatment.
 - e. Complaint from a participant or about others, when the complaint indicates unexpected risks or cannot be resolved by the research team.
 - f. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
 - g. Breach of confidentiality (i.e. disclosure of Private Health Information or participant identifiers, equipment containing research data, missing or stolen research records, access of information by unauthorized individuals).
 - h. Any event under the jurisdiction of the Campus IRB (including on-site and off-site), adverse event, injuries, side effects, deaths, or other problems), which in the opinion of the principal investigator was 1) unanticipated; 2) involved risk to the participants or others, and 3) was related to research procedures;
 - i. Any event that requires prompt reporting according to the sponsor;
 - j. Any accidental or unintentional change to the IRB approved proposal that involved risks or has the potential to recur;
 - k. Any deviation from the approved proposal (protocol violation) that are related to participant safety, significant new findings, or a defined subset of adverse events;
 - l. A paper is published from another study that shows that an arm of your research study is of no therapeutic value
 - m. A paper published from another study that shows the risks or potential benefits of the research may be different than initially presented to the IRB.
 - n. Change to the protocol taken without prior IRB review to an eliminate apparent immediate hazard to a research participant
 - o. Any independent safety monitoring reports or DSMB reports;
 - p. Breach of confidentiality of research data;
 - q. Breach of privacy, confidentiality, data security, loss of study data and destruction of study data due to noncompliance;
 - r. Incarceration of a participant in a protocol not previously approved by the IRB to enroll prisoners.

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

- s. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) caused harm to participants or others or indicates that participants or others are at increased risk of harm.
- t. Unanticipated adverse device effect (Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.)
- u. Any complaint of a participant that indicates an unanticipated risk or that can't be resolved by the research team;
- v. Information that indicates a change to the risks or potential benefits of the research:
 - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected
 - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected
 - An interim analysis or safety monitoring report that indicates the frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - 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;

The investigator should contact the Campus IRB if unsure whether the event should be reported.

B. Step 2 Campus IRB: Initiate an inquiry

The Campus IRB will initiate an inquiry into learned, suspected, alleged, or questionable unanticipated problems or event WITHIN 5 BUSINESS DAYS OF RECEIPT OF NOTICE. An inquiry may consist of, but not limited to, any investigative fact finding methods that probe into the possible unanticipated problem or event and may aid in the determination of a finding.

APPROACH

The Campus IRB Compliance Officer or Board Chair shall have the authority to initiate an inquiry into an unanticipated event, and may determine if immediate action is needed to ensure the participant's safety and suspend some or all of the research pending review of the event at the next convened IRB meeting. Administrative holds or Suspensions will comply with the Campus IRB "Suspension and Termination of IRB Approval" policy.

- a. The Campus IRB Compliance Officer or Board Chair shall have the authority to designate the appropriate resources to conduct an initial review to determine if previous or current participants are placed at risk.
- b. The Campus IRB shall have the authority to access any information from the research team through an audit or investigation to facilitate the investigation resolution objective.

- C. Step 3 Make a determination of findings.** The investigation process shall result in a determination of finding of 1) whether the problem or event is an unanticipated problem involving risk to participants or others; or 2) Whether the event or problem is not an unanticipated problems involving risks to participants or others.

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

The Campus IRB Chair or Compliance Officer's "finding" determination will be the result of a fact-finding investigation according to this policy, based upon:

1. Step 1: Conducting an initial review of the problem or adverse event report submitted by the investigator via the eIRB system, investigative materials and any supportive information that assists the decision-making process of whether participants were placed at risk.
2. Step 2: The determination of whether the problem or adverse event is an unanticipated problem involving risk to participants or others can be made by the Campus IRB Chair, Campus IRB Compliance Officer, or a convened Campus IRB.
3. Step 3: If the Campus IRB deems the activity to NOT be an unanticipated problem involving risk to participant or others, the Campus IRB will communicate to the investigator in writing in accordance with its policies and procedures; AND no further action is taken under this policy.
 - a. If the problem is determined by the Campus IRB Compliance Officer or Board Chair to be an unanticipated problem involving risks to participants or others, the unanticipated problem involving risk to participants or others is reviewed by the convened IRB following Step 5.

ACTIVITIES REQUIRING REVIEW BY THE CONVENEED IRB

D. STEP 5: REVIEW BY THE CONVENEED CAMPUS IRB

The Campus IRB policies require the investigator to address unanticipated problems involving risks to research participants or others to employ procedures to minimize risks. The investigator is REQUIRED TO REPORT ALL PROBLEMS DESCRIBED IN THE ABOVE REPORTING REQUIREMENTS

Activities requiring review by the convened IRB:

- ALL problems determined by the Campus IRB Compliance Officer or Board Chair to be unanticipated problems involving risk to any participant or others.
- ALL board members will receive a copy of the Unanticipated Problems or Adverse Event form and all documents related to the research proposal and event, including the IRB protocol, initial application, the consent document, and the Corrective Action Plan proposed by the investigator."

Step 1: CAMPUS IRB REVIEW PROCESS (Convened Board)

The matter must be docketed on the next available convened board meeting in compliance with the following policies:

- Campus Institutional Review Board Authority
- Board Meeting Procedures
- Minutes
- Invitees: Requesting Information from Prisoner Advocates, Consultants and Guests
- Record Keeping Process
- Investigator or Key Personnel Responsibilities
- Campus IRB Review Process
- Assessing the Level of Risk
- Unanticipated Problems or Adverse Events Review Process
- Noncompliance with Campus IRB Policies and Procedures
- Suspension and Termination of IRB Approval
- Campus Institutional Review Board Reporting Requirements

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

- Quality Assessment and Improvement
- Deviation Review Process
- Complaint Procedures

The event will be reviewed in accordance with the Campus IRB “Review Process” policy primary reviewer system.

- All board members will receive a copy of the Unanticipated Problems or Adverse Event form and all documents related to the research proposal and event, including the Corrective Action Plan proposed by the investigator.
- All board members will have full access to the record and all associated proposal documents and IRB correspondence *unless* they are a member of the team or have a Conflict of Interest. The review will be conducted in accordance with the “Conflict of Interest” policy if applicable.

The convened board will:

1. Review the Corrective Action Plan (CAP) to assess the appropriateness of the plan in protecting the subjects;
2. Determine if the status of the project should remain active, be modified, suspended or terminated;
3. Determine if the Recruitment Process needs to be modified.
4. Determine if the Consent Process needs to be modified.
5. Determine if subject participants require supplemental information;
6. Determine if the matter is affected by State, Federal, and Local Law and may contact General Counsel, when necessary to assure compliance.
7. Require the Campus IRB to provide a comprehensive review of the status of the project to determine if revisions are necessary;
8. Make a decision (See ACTIONS below). Deliberate and vote in accordance with the “Board Meeting Procedures” policy and procedures.
9. Conduct an audit evaluation of the research project, if necessary;
10. Decrease the approval period interval, if necessary; and
11. Require monitoring and reporting from the investigator(s), if necessary.
12. Make any determination necessary to protect the safety and welfare of human subject participants.
13. Suspension of the research pending a more thorough review (in accordance with the Campus IRB Review Process policy.)
14. Termination of the study (in accordance with the Campus IRB Review Process policy.)
15. The Campus IRB (or designee) will report unanticipated problems involving risks to participants or others to the Institutional Official and applicable regulatory authorities such as OHRP and FDA, within 30 days of the event, in accordance with the “Reporting Policy”. When appropriate, the Office of the General Counsel, department head, and others may be notified in accordance with this Policy.

E. NOTIFICATION TO THE INVESTIGATOR

- No action required: If the event or problem is not deemed to be an unanticipated problem involving risks to participants, the investigator will receive written notice indicating that the IRB has reviewed the report and determined that no action will be taken.
- Action: Convened IRB Committee Review: The Campus IRB will notify the investigator in writing as soon as possible, but no later than 5 business days of the determination that the matter is an unanticipated problem involving risk to participants or others. The investigator will be notified of the date of the convened meeting and any additional information or individuals required to appear before the board. If applicable,

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

the event will be reported to the appropriate individuals and agencies in accordance with the Campus IRB "Reporting Requirements" Policy. This report will be disseminated to the IRB members at the next convened IRB meeting.

F. CAMPUS IRB REPORTING REQUIREMENTS

The Campus IRB must ensure distribution of a written report of all unanticipated problems involving risks to participants or others, non-compliance determined to be serious or continuing, and suspensions and terminations of approved research by the IRB to the categories below within (30) days, and in all cases of death within 24 hours:

1. Institutional Officials

The Vice-Chancellor for Research is the designated recipient of the report.

2. Governmental Agencies

The head of any supporting Federal department or agency, OHRP, and any other relevant regulatory entity or unit governing the research shall receive the written report.

3. Sponsors or Coordinating Centers

The head of any coordinating center or sponsor supporting the research may receive a written report upon request.

G. IRB REPORT DOCUMENTATION

The Vice-Chancellor for Research has the institutional responsibility for overseeing the IRB human subject research program processes and is responsible for assuring the Campus IRB operations are conducted in compliance with governing regulations and laws. The Vice-Chancellor for Research in coordination with the Campus IRB Compliance Officer and IRB Chair will notify, when appropriate, the individuals and/or agencies.

The Vice-Chancellor for Research may delegate the report preparation responsibility to the Campus IRB. The Campus IRB Chair and Compliance Officer, or designee shall assure the aforementioned report contains the following information:

1. The nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of approval of research)
2. Name of the institution conducting the research
3. Title of the research project and/or grant proposal in which the problem occurred.
4. Name of the principal investigator on the protocol
5. Identifying IRB Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
6. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
7. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)

Unanticipated Problems or Adverse Events Involving Risks to Participants and Others
Policy Number 2876.32

8. Distribute the report:

The Campus IRB or designee send a copy of the report to:

- i) The convened Campus IRB by including the report on the next agenda
 - ii) The Office of Research – Vice Chancellor of Research
 - iii) The appropriate Institutional Officials
 - iv) The following agencies, *when applicable*:
 - (1) OHRP, if the study is subject to DHHS regulations or subject to a DHHS federal-wide assurance
 - (2) If the study is conducted or funded by any Federal Agency other than DHHS that is subject to “The Common Rule”, the report is sent to OHRP or the head of the agency as required by the agency
 - (3) Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.
 - v) Principal investigator and Department Chair
 - vi) Sponsor, *when applicable*.
 - vii) Contracted research organization, *when applicable*
 - viii) The Privacy Officer of a covered entity, *when applicable* (if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity)
 - ix) The Information Security Officer of an organization, *when applicable* (if the event involved violations of information security requirements of that organization)
 - x) Any applicable Institutional Offices or Units,
 - xi) The Campus IRB Compliance Officer can provide copies to others as deemed appropriate
9. The Campus IRB Compliance Officer will ensure that all steps of this policy will be completed within 30 business days of the initiating action.
10. The Campus IRB Compliance Officer will assure that the appropriate documentation is recorded in the IRB records and maintained for a period of 3 years after withdrawal, closure of research activities, expiration of approval, or the cessation of activities.

H. ADDITIONAL APPLICABLE POLICIES REQUIRING COMPLIANCE

The investigator shall comply with the additional policies listed below in accordance with the Campus IRB policies and procedures:

- Campus Institutional Review Board Authority
- Board Meeting Procedures
- Minutes
- Invitees: Requesting Information from Prisoner Advocates, Consultants and Guests
- Record Keeping Process
- Investigator or Key Personnel Responsibilities
- Campus IRB Review Process
- Assessing the Level of Risk
- Unanticipated Problems or Adverse Events Review Process
- Noncompliance with Campus IRB Policies and Procedures
- Suspension and Termination of IRB Approval
- Campus Institutional Review Board Reporting Requirements
- Quality Assessment and Improvement
- Deviation Review Process
- Complaint Procedures

Revised December 2006

Revised June 2007

Revised November 2007

Revised February 2008