KEY INVESTIGATOR RESPONSIBILITIES

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Agenda

- Review Investigator Responsibilities
- Discuss change from Protocol Deviation to Non-Compliance with the Protocol
- Review Adverse Event Definitions
- Examine reporting scenarios
- Q & A

PI Responsibilities

- In a nutshell, the PI is responsible for:
  - Human Subject Protection
  - Training
  - Conflict of Interest
  - IRB Approval
  - IND/IDE
  - Study Conduct
  - Informed Consent
  - Amendments
  - Continuing Review
  - Data Safety Monitoring
  - Adverse Events
  - Complaints
  - Record Retention
  - GINA

In other words…EVERYTHING!

General Responsibilities of Investigators (VI.B.1)

- **Subject: Procedure for General Responsibilities of Investigators**

  Procedure:
  This procedure outlines the general responsibilities of Investigators conducting research involving humans.

  I. Investigator Responsibilities.

- A. The **Investigator will obtain knowledge** regarding federal, state, and local laws and regulations, institutional policies, IRB policies and procedures, the ethical principles of *The Belmont Report*, and Good Clinical Practice (GCP) Guidelines, if applicable, prior to conducting research involving humans.

- B. The **Investigator will assure protection of the participant's rights and safety** by adequate design and conduct of research, as well as oversight of all research processes and procedures and other research personnel involved in research activities.

- C. The **Investigator will apply for IRB review and approval** according to IRB policies and procedures prior to conducting human subjects research.

General Responsibilities of Investigators

- D. The **Investigator will complete the required IRB training** through the University of Miami Collaborative IRB Training Initiative (CITI). Instructions and access to training is available on the IRB Website at http://www.mc.vanderbilt.edu/irb/ in the left column under “Education and Training” and “VU Human Subjects Training Program.” The **Investigator will assure that all key study personnel (KSP) have completed the required IRB training** prior to IRB submission of research applications. In addition, the Investigator will participate and assure that all KSP participate in continuing education at least annually as required by IRB policy.

- E. The **Investigator will respond to all IRB requests** for additional information in regards to verifying knowledge, training, and resources adequate to perform research involving human participants.

General Responsibilities of Investigators

- F. The **Investigator will assure that required approvals from other university committees or institutions are granted** prior to beginning research activities.

- G. The **Investigator will assure the proper handling, storage, and dispensing of all investigational agents** and when not using the services of the Investigational Drug Service (*See* IRB Procedure XI.B.1 for proper procedure).

- H. **The Investigator will disseminate new information** regarding the use of FDA agents in research to participants as he/she becomes aware.

Training

- PI must complete initial and annual VU IRB human research protections training.

- It is also the responsibility of the PI to assure that other Investigators and key study personnel who are responsible for the design and conduct of the research are adequately trained in human research protections and completion of continuing education requirements.

Training

- The PI is also responsible for ensuring that all individuals conducting the research are adequately qualified and licensed to perform the research related procedures.

- In 2008, the VU IRB sent a letter to Investigators after OHRP sent a determination letter to an IRB and PI citing them for “failing to meet 45 CFR 46.111(a)(1),” which states that risks to subjects are minimized.

Study Conduct

- Investigators responsibilities during the conduct of an approved research study include:
  - Obtaining and documenting informed consent of subjects or subjects' legally authorized representative PRIOR TO the subjects' participation in the research unless the IRB has approved a waiver of consent.

Study Conduct

- Obtaining prior approval from the IRB for **any** modifications of the previously approved research, except those necessary to eliminate apparent immediate hazards to the subject(s).

- Ensuring progress reports and requests for continuing review and approval are submitted to the IRB in accordance with IRB P&P's, and the institution's Federal Wide Assurance.

Study Conduct

- Providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others.
- Providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB.

Informed Consent Process

- Continuous process
  - The Investigator assures the informed consent process in research is an ongoing exchange of information between the research team and the study participants throughout the course of a research study. Informed consent is a continuous process of communication and acknowledgement over time, not just a signed document.
- Free from coercion and undue influence
  - An Investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
- Documentation
  - Provide document for review
  - Questions
  - Verbalizes Understanding

Elements of Informed Consent

Required

- Research (Purpose/Duration/Procedures)
- Risks/discomforts
- Benefits
- Alternatives
- Confidentiality
- Whom to contact
- Compensation/ treatment for research related injury
- Right to refuse or withdraw
- FDA element for clinicaltrials.gov

Additional

- Unforeseen risks to subject (fetus)
- Anticipated reasons for termination from the study by PI
- Costs
- Consequences of withdrawal by participant
- New findings
- Number of subjects

Documentation:

- Should be legible, factual and thorough.

- Should include items such as when the person:
  - was initially provided information about the study;
  - was given a copy of the consent form;
  - was contacted to determine interest; and
  - signed the document.

- Include details of special situations.

Privacy/Confidentiality Issues

- How will the privacy and confidentiality of participants be protected?
- Will data be coded, stored in a password protected computer?
- Who has access to the code?
- Is information being shared with other Investigators or institutions?
- Have all HIPAA requirements been met?

Amendments

- Any changes to the IRB approved research must be submitted, reviewed, and approved by the IRB PRIOR to implementation.

- The only time the investigator may make a modification to research activities without prior IRB approval is to avoid an immediate hazard to the participant. The PI must report the event to the IRB within 10 working days.

- The Request for Amendment form is no longer listed as a form on the IRB website. To create an amendment, log into DISCOVR-E and click the “Create Submission” button located on the upper right corner.

WHY NONCOMPLIANCE WITH THE PROTOCOL?

So Why Noncompliance?

- There are specific regulations established by the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) under which the IRB must function.

- The term “protocol deviation” is not recognized within the regulations that govern IRB function.

- The Vanderbilt Human Research Protection Program (VHRPP) is an accredited program.
- As a result, the VHRPP must undergo periodic re-accreditation.
- As part of the re-accreditation process, we are given recommendations for our program.

- At our most recent re-accreditation visit, it was recommended that the term “protocol deviation” be changed to align with the language used by the federal regulations.
- What does this mean to you … nothing. It is simply a wording change, reporting requirements and procedures have not changed.

DEFINITION

Definition of Noncompliance

- Noncompliance
  - An incident involving non-adherence to the approved protocol.
  - Non-compliance is an unplanned and unintended change to the protocol. It does not occur as a deliberate, purposeful change to an approved protocol.
- It may result from the actions of the participant, investigator, or study personnel.

- What is a deliberate, purposeful change to the protocol?
- An amendment.
- Is an exception deliberate and purposeful?

- Is an investigator allowed to deviate from the protocol to prevent an immediate hazard to the participant?

- Yes.

- As a means of reporting this type of event the “Non-Compliance with the Protocol Form” may be used.

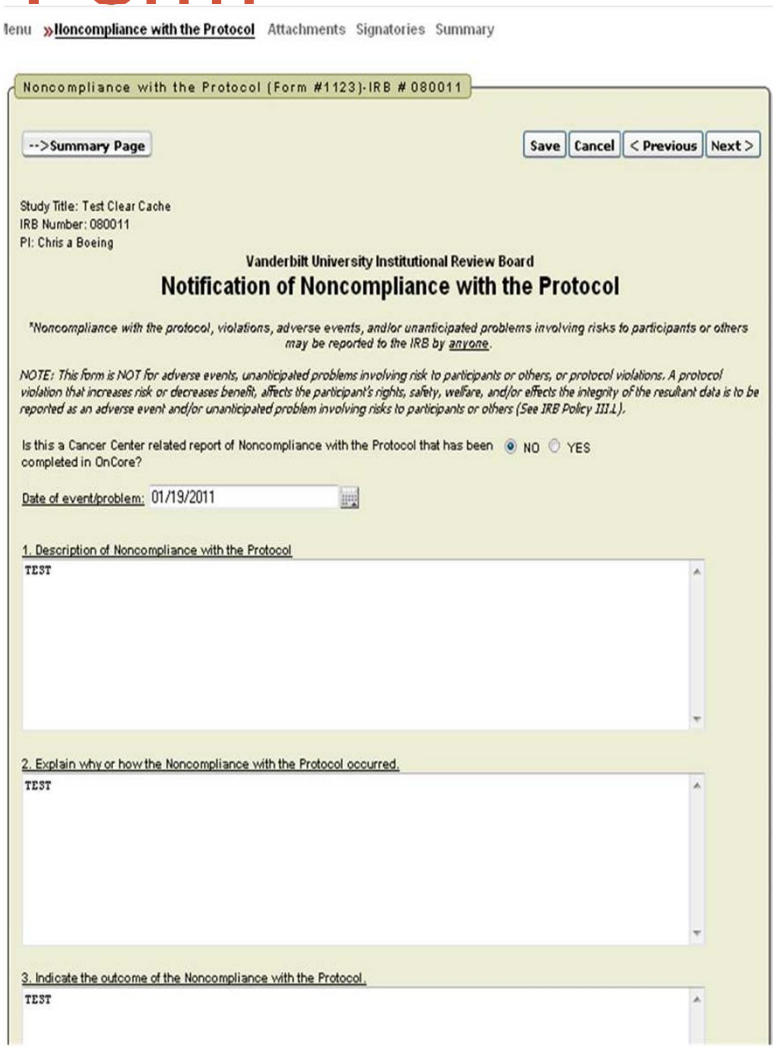
When Is It Necessary to Report Non-compliance with the Protocol to the IRB on the “Notification of Noncompliance with the Protocol Form” (formerly protocol deviation)?

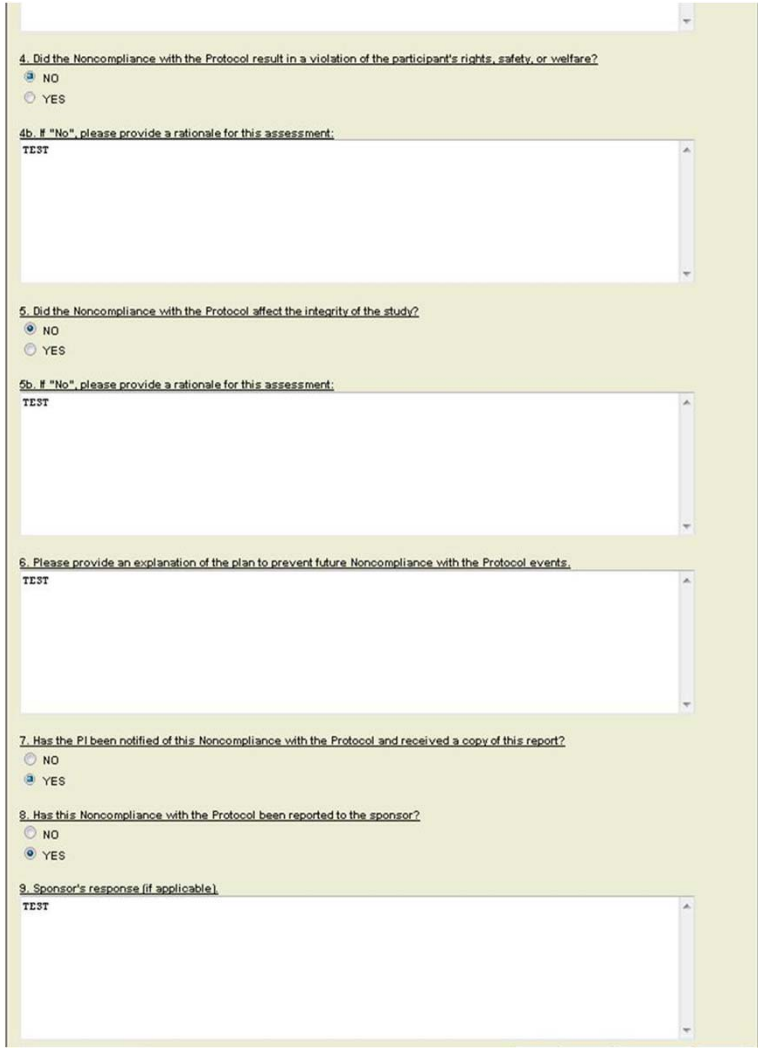
- When the Sponsor requests the IRB be notified.

- When the protocol defines IRB reporting obligations.

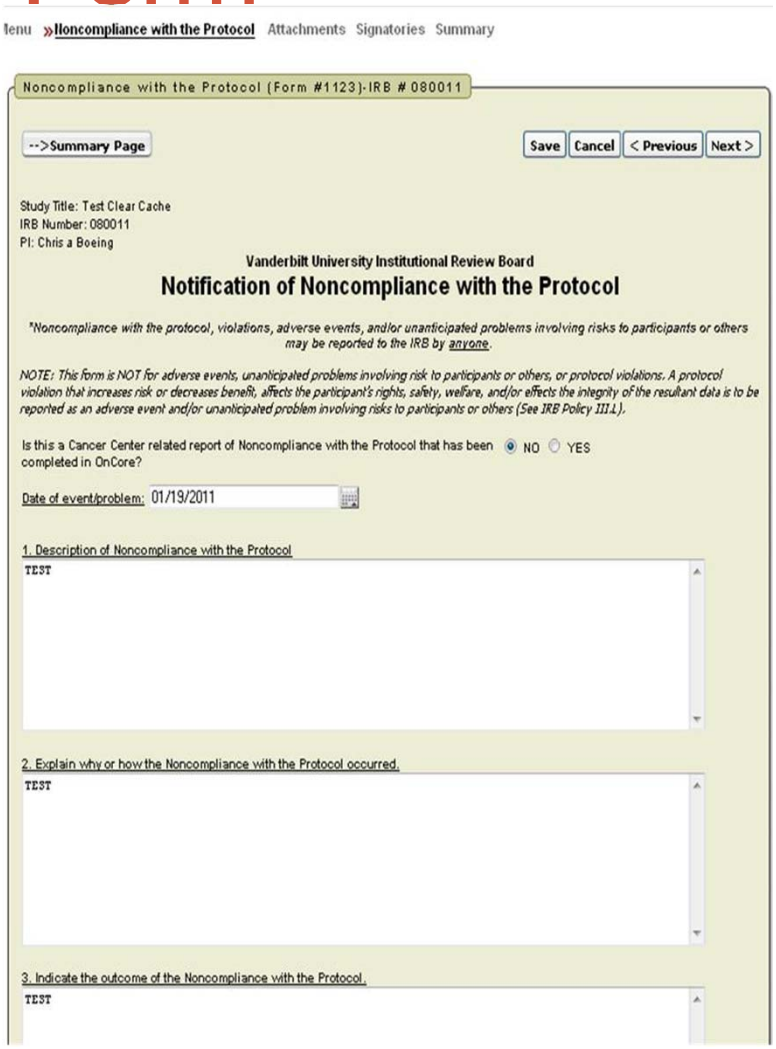
- If the sponsor does not request events of non-compliance with the protocol be reported, and the protocol does not define IRB reporting obligations for these events, when should they be reported?
- Events of non-compliance with the protocol that are not required to be reported by the sponsor or protocol should be reported at the time of continuing review in a summary format.

The Form


Menu »Noncompliance with the Protocol Attachments Signatories Summary
Noncompliance with the Protocol (Form #1123)-IRB # 080011
-->Summary Page
Save Cancel < Previous Next >
Study Title: Test Clear Cache
IRB Number: 080011
PI: Chris a Boeing
Vanderbilt University Institutional Review Board
Notification of Noncompliance with the Protocol
*Noncompliance with the protocol, violations, adverse events, and/or unanticipated problems involving risks to participants or others may be reported to the IRB by anyone.
NOTE: This form is NOT for adverse events, unanticipated problems involving risk to participants or others, or protocol violations. A protocol violation that increases risk or decreases benefit, affects the participant's rights, safety, welfare, and/or effects the integrity of the resultant data is to be reported as an adverse event and/or unanticipated problem involving risks to participants or others (See IRB Policy III.L).
Is this a Cancer Center related report of Noncompliance with the Protocol that has been completed in OnCore? NO YES
Date of event/problem: 01/19/2011
1. Description of Noncompliance with the Protocol
TEST
2. Explain why or how the Noncompliance with the Protocol occurred.
TEST
3. Indicate the outcome of the Noncompliance with the Protocol.
TEST


4. Did the Noncompliance with the Protocol result in a violation of the participant's rights, safety, or welfare?
NO
YES
4b. If "No", please provide a rationale for this assessment:
TEST
5. Did the Noncompliance with the Protocol affect the integrity of the study?
NO
YES
5b. If "No", please provide a rationale for this assessment:
TEST
6. Please provide an explanation of the plan to prevent future Noncompliance with the Protocol events.
TEST
7. Has the PI been notified of this Noncompliance with the Protocol and received a copy of this report?
NO
YES
8. Has this Noncompliance with the Protocol been reported to the sponsor?
NO
YES
9. Sponsor's response (if applicable).
TEST

The Form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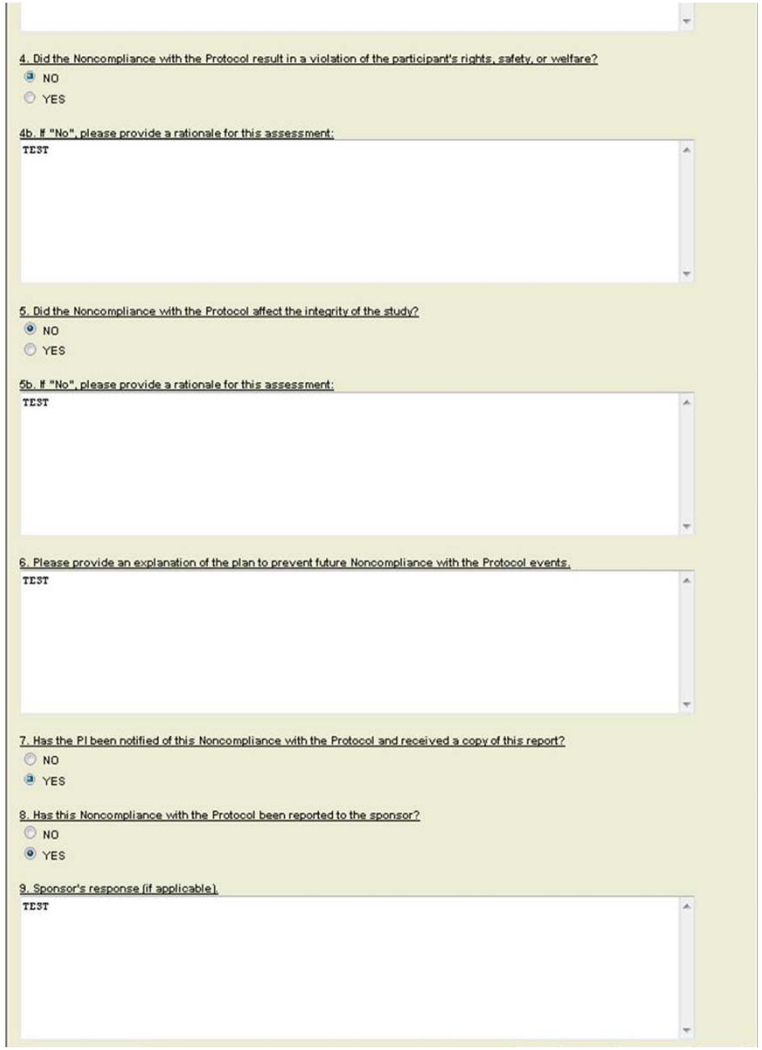
Date of event/problem: 01/19/2011
1. Description of Noncompliance with the Protocol
TEST
2. Explain why or how the Noncompliance with the Protocol occurred.
TEST
3. Indicate the outcome of the Noncompliance with the Protocol.
TEST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NO
YES
4b. If "No", please provide a rationale for this assessment:
TEST
5. Did the Noncompliance with the Protocol affect the integrity of the study?
NO
YES
5b. If "No", please provide a rationale for this assessment:
TEST
6. Please provide an explanation of the plan to prevent future Noncompliance with the Protocol events.
TEST
7. Has the PI been notified of this Noncompliance with the Protocol and received a copy of this report?
NO
YES
8. Has this Noncompliance with the Protocol been reported to the sponsor?
NO
YES
9. Sponsor's response (if applicable).
TEST

When should this be reported?

- A study nurse realizes the consent form signed by the participant is not the most recent version, but the consent form has not expired.

When should this be reported?

- The investigator enrolled a participant on trial with a PTT of 15 seconds. The study criteria requires a PTT of 10 to 12 seconds. The study drug is not known to cause bleeding problems.

- In the same study in the previous scenario, this noncompliance with the protocol has been reported 3 times.

- What does the PI need to consider?

ADVERSE EVENTS

Federal Definition - OHRP

- **Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:**
- 1) unexpected (in terms of nature, severity, or frequency);
- 2) related or possibly related to participation in the research; and
- 3) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

OHRP

- OHRP notes that an incident, experience or outcome that meets these three criteria will warrant consideration of substantive change in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare or rights of subjects or others.

OHRP

- Examples of corrective actions or substantive changes may include:
  - Changes to the protocol
  - Modification of the inclusion/exclusion criteria
  - Implementation of additional monitoring procedures
  - Suspension of enrollment of new subjects or research procedures in enrolled subjects
  - Providing additional information about newly recognized risks to enrolled subjects

Federal Definition - FDA

- Unexpected Adverse Event
  - FDA defines this as any event where:
    - 1) the specificity or severity of which is not consistent with the current Investigator Brochure (IB); or
    - 2) if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Federal Definition - FDA

- Serious Adverse Event
  - FDA defines a serious adverse event as an event that results in any of the following outcomes:
    - death;
    - a life-threatening adverse event;
    - inpatient hospitalization or prolongation of existing hospitalization;
    - a persistent or significant disability/incapacity;
    - a congenital anomaly/birth defect; or
    - requires intervention to prevent permanent impairment or damage.

IRB Definition (Policy III.L)

- Unanticipated Problems Involving Risk to Participants or Others
  - Any event that was:
    - 1) unanticipated;
    - 2) related; and
    - 3) places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Why Do We Report?

- OHRP (Office of Human Research Protections) and the FDA (Food and Drug Administration) require reporting of serious adverse events and unanticipated problems involving risk to participants and others.

- Serious adverse events and unanticipated problems must be reported in order to continually assess the risk(s) associated with participation in a study.

VU IRB Reporting

- IRB Policy III.L states a serious adverse event, injury, side effect, death or other problem **occurring at VU or other location in which the Investigator is responsible for the conduct of the research AND the VU IRB serves as the IRB of Record** must be reported**.**

OHRP Reporting

- 45 CFR 46.103(a) and (b)(5) require that institutions have written procedures to ensure the following incidents related to research conducted under an OHRP – approved assurance are promptly reported to OHRP:

1. Any unanticipated problems involving risks to subjects or others;
2. Any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and
3. Any suspension or termination of IRB approval.

OHRP Reporting

- Example of Adverse Event FAL Language
  - *The Committee has accepted the reported Adverse Event and determined that no changes to the protocol or consent form(s) are needed at this time. However, please note that this event requires reporting to the Office for Human Research Protections (OHRP) due to its categorization as a serious adverse event (SAE) per IRB Policy III.L. Reporting of Adverse Events, Serious Adverse Events and Unanticipated Problems Involving Risk to Participants or Others. This report is initiated by the Institutional Review Board (IRB) and, thus, requires no further action on your part at this time. You will receive a copy of this report for your records when it has been finalized.*

FDA/OHRP Reporting

- The IRB letter sent to the agency will outline:
  - the nature of the event;
  - the findings of the organization and IRB;
  - actions taken by the organization or IRB;
  - reasons for the organization’s or IRB’s actions; and
  - plans for continued investigation or action.

What to Report

- Any serious event that in the Investigator's opinion was unanticipated or unexpected, involved risk to participants or others and was possibly related to the research procedures;

What to Report

- Any deviation from the IRB-approved protocol that increased the risk or affected the participant’s rights, safety, or welfare.

When to Report

- Serious and unanticipated events must be reported to the VU IRB within 10 working days of the Investigator's knowledge.

- Events that do not occur at VU or a location in which the Investigator is responsible for the conduct of the research and VU is not the IRB of Record should be reported in a summary format at the time of continuing review, **unless…**

When to Report

…the event is serious, related, and unanticipated.

In these cases, the event should be reported on a Request for Amendment form and include the Sponsor's or DSMB's assessment of the event and the VU PI's assessment.

The amendment should also include any revision to the approved protocol to incorporate the event's impact on the risk-potential benefit profile of the study.

SCENARIOS

Should this be reported?

- A participant takes a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Medical evaluation reveals gastric ulcers. The protocol and ICD state there is a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers if assigned to the active agent.

Should this be reported?

- YES, but at the time of continuing review.
  - This is not an unanticipated problem because the occurrence of gastric ulcers in terms of nature, severity, and frequency was expected.

Should this be reported?

- A participant with advanced renal cell carcinoma enrolls in a study evaluating the effects of hypnosis for the management of chronic pain. During the initial session, the participant develops acute chest pain, SOB, followed by loss of consciousness. The participant suffers a cardiac arrest and dies. The autopsy reveals the participant died of a massive pulmonary embolus related to the renal cell carcinoma.

Should this be reported?

- YES (IRB)
  - This is not an unanticipated problem because the subject's pulmonary embolus and death were attributed to causes other than the research intervention.

Should this be reported?

- Due to a processing error by a pharmacy technician, a participant receives a dose of an experimental agent that is 10-times higher than the dose stated in the IRB approved protocol. While the dosing error increased the risk of toxicity, the participant experienced no detectable harm or adverse effects.

Should this be reported?

- YES (IRB/Sponsor/OHRP/FDA)
  - This is an unanticipated problem that needs to be reported because the incident was:
    - Unexpected
    - Related to study participation
    - Placed the subject at a greater risk of physical harm

Should this be reported?

- An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data is stored on a laptop computer which is stolen from the PI’s car on the way home from work.

Should this be reported?

- YES (IRB/OHRP)
  - This is an unanticipated problem that needs to be reported because the incident was:
    - Unexpected (theft was unanticipated)
    - Related to study participation
    - Placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality than was previously known or recognized

Should this be reported?

- Cancer patients are enrolled in a Phase II trial evaluating an investigational product derived from human sera. After several ppt's are enrolled, an audit reveals the investigational product was obtained from donors who were not appropriately screened and tested for several potential viral contaminants including the human immunodeficiency virus and hepatitis B virus.

Should this be reported?

- YES (IRB/Sponsor/OHRP/FDA)
  - This is an unanticipated problem that needs to be reported because the incident was:
    - Unexpected
    - Related to study participation
    - Placed the subject AND POSSIBLY OTHERS at a greater risk of physical harm

Should this be reported?

- Subject #5 in a study of a new oral agent administered daily for the treatment of severe psoriasis develops severe hepatic failure complicated by encephalopathy one month after starting the study medication. The known risk profile includes mild elevation of serum liver enzymes in 10% of subjects receiving the agent, but no other history of participants developing clinically significant liver disease.

Should this be reported?

- YES (IRB/Sponsor/OHRP/FDA)
  - This is an unanticipated problem that needs to be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was:
    - Unexpected in severity
    - Possibly related to participation in the research
    - Serious

Should this be reported?

- A PI is conducting a study evaluating factors that affect reaction times in auditory stimuli. To perform the reaction time measurements participant's are placed in a small, windowless soundproof booth and asked to wear headphones. A subject experiences significant claustrophobia and withdraws from the research. The protocol and ICD describe claustrophobic reactions as one of the risks associated with the research.

Should this be reported?

- YES, but at the time of continuing review.
  - This is not an unanticipated problem because the occurrence of claustrophobic reactions in terms of nature, severity, and frequency was expected.

Resources

- Office for Human Research Protections (OHRP)
  - http://www.hhs.gov/ohrp/
- Food and Drug Administration (FDA)
  - http://www.fda.gov/
- Institutional Review Board (IRB)
  - http://www.mc.vanderbilt.edu/irb/
- Good Clinical Practice
  - http://www.fda.gov/oc/gcp/guidance.html
  - http://www.citiprogram.org
- International Conference on Harmonisation
  - http://www.ich.org/

Questions

Questions? Comments? Concerns?

- For future questions you may contact

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