Reportable New Information (RNI)

IRB Policies and Procedures Chapter 17

HHS Regulatory Requirements

Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others [45 CFR 46.103(b)(5)]

For research covered by an assurance approved for federal-wide use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

General Overview of Reporting Requirements

- **Unanticipated Problem Involving Risk to Human Subjects or Others**: Events that may meet the definition of an Unanticipated Problem Involving Risk to Human Subjects or Others must be reported to the IRB as Reportable New Information
- **Adverse Events that are Unanticipated Problems Involving Risk to Human Subjects or Others**: Adverse Events (medical occurrences) that meet the definition of an Unanticipated Problem Involving Risk to Human Subjects or Others must be reported to the IRB as Reportable New Information.
- **Reportable Non-compliance**: Incidents of Non-compliance (including protocol deviations) that may meet any of the definition of Serious Non-compliance and/or Continuing Non-compliance must be reported to the IRB as Reportable New Information

University of Pittsburgh Policy

Require reporting of Adverse events and unanticipated events which meet the definition of an "unanticipated problem involving risks to human subjects or others"

Investigator

Require reporting of non-compliance which

- Significantly adversely affects the rights or welfare of participants, or
- Significantly compromises the quality of the research data, or
- May represent serious and/or continuing non-compliance or is otherwise deemed reportable to the IRB

Review reports of non-compliance and determine which constitute serious or continuing non-compliance and/or an unanticipated problem involving risk to human subjects or others

Fulfill reporting requirements to the appropriate entities (institutional officials, federal departments or agencies)

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IRB

Definitions:

Adverse Event

Any unfavorable **medical** occurrence in human subjects, including abnormal signs

- (e.g., abnormal physical exam or laboratory findings), symptoms, or disease temporally associated with, but not necessarily considered related to, the subject's participation in the research.

Unanticipated Problems Involving Risk to Subjects or Others (UAP)

Any incidence, experience, or outcome that meets all of the following criteria:

- **Unexpected** in terms of nature, severity, or frequency
- **Related or possibly related** to participation in the research
- Suggest that the research **places subjects or others at a greater risk of harm** (including physical, psychological, economic or social harm) than was previously known or recognized

Examples of Reportable UAPs Involving Risks to Subjects or Others

- Any accidental or intentional deviation from the IRB-approved protocol that involves potential serious risks (e.g., missed safety labs, incorrect dosing, or labeling.
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a given research subject.
- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected increase in the risk to benefit ratio of the research.
- Any complaint or concern of a subject that indicates an unanticipated risk or cannot be resolved by the research staff.
- Any other untoward event that affects the welfare or the privacy, confidentiality or other rights of research subjects or members of their family (e.g. lost or stolen research data).
- Any other untoward event that presents a risk to Investigators and research staff involved in the conduct of the research

Definitions: Adverse Events (AE)

External Adverse Event:
An Adverse Event that occurs at a site external to the authority of the University IRB and is reported to the University or UPMC investigator

Internal Adverse Event:
An Adverse Event that occurs at a site that falls directly under the authority of the University IRB

Definitions: Relationship to Research

Possibly Related to the Research Intervention:

In the opinion of the Principal Investigator, there is a reasonable possibility that the incident, experience, new information or outcome may have been caused by the procedures involved in the research

Probably Related to the Research Intervention:

In the opinion of the Principal Investigator, the incident, experience, new information or outcome more likely than not was caused by the procedures involved in the research

Non-Compliance Definitions

- **Serious non-compliance**: Non-compliance that, in the judgment of the University IRB, significantly adversely affects the rights or welfare of participants, or significantly compromises the quality of the research data.
- **Continuing non-compliance**: Non-compliance that has been previously reported or a pattern of ongoing non-compliance that, in the judgment of the University IRB, significantly adversely affects the rights and welfare of participants or significantly compromises the quality of the research data

Incidents of Reportable of Non-Compliance

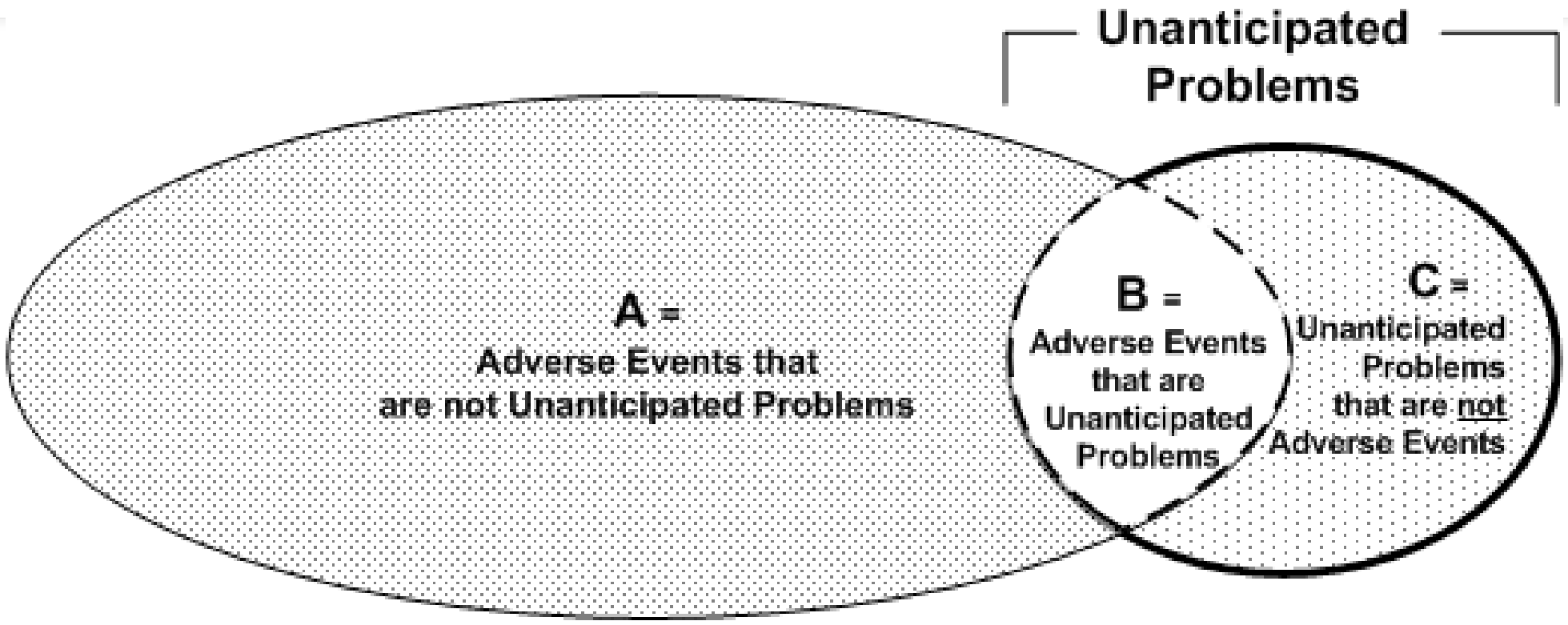
Failure on the part of the Investigator or any member of the study team to follow the terms of IRB approved study application or to abide by applicable laws or regulations, or HRP policies that may:

- Significantly adversely affect the safety, rights, or welfare of human subjects; OR
- Significantly compromise the quality or integrity of the research data (i.e., negatively impacts the ability to draw conclusions from the study data); OR
- Represent Continuing Non-compliance (i.e., has been previously reported or represents a pattern of ongoing non-compliance).

Examples of Reportable Non-Compliance

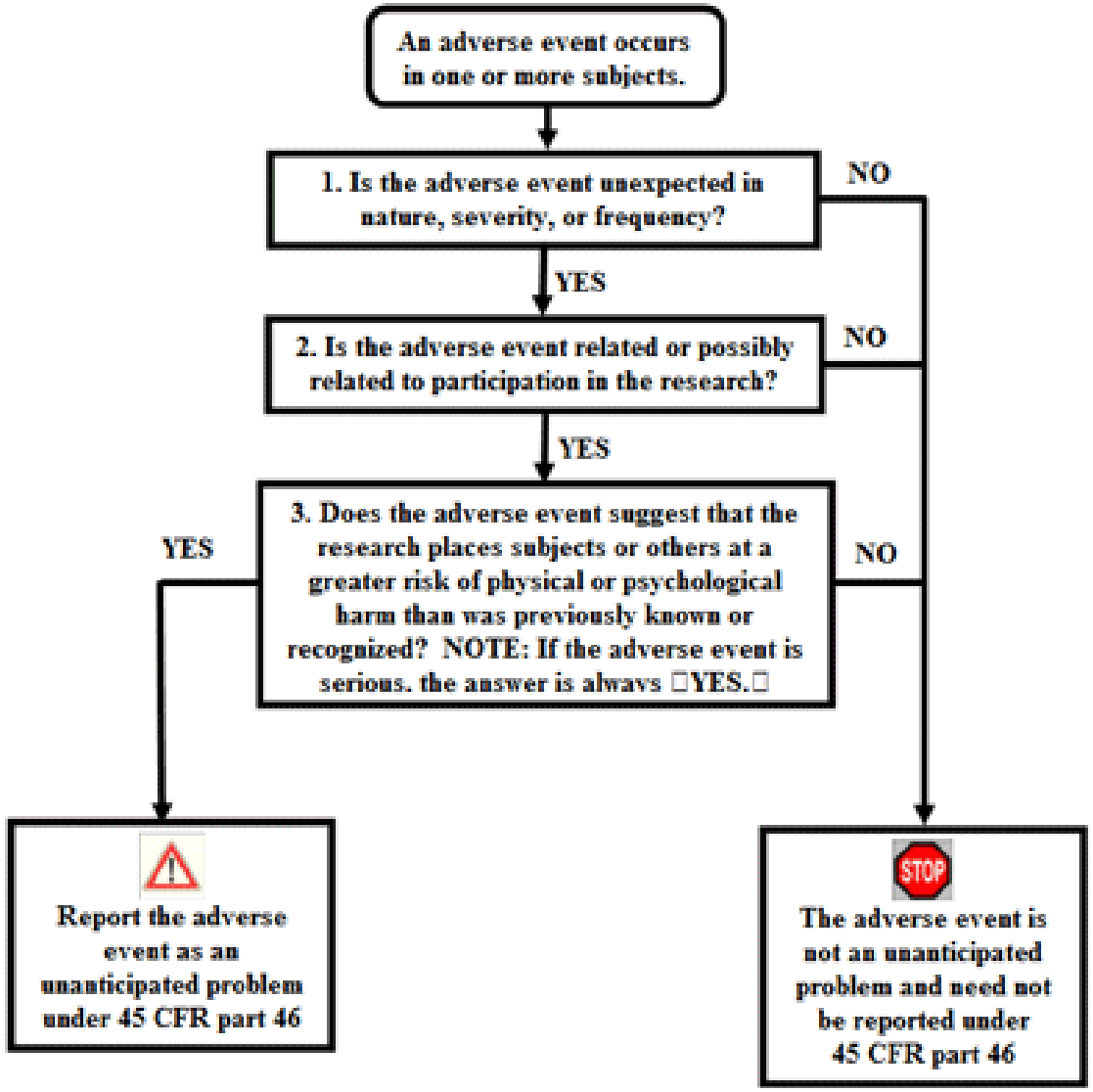
- Performing non-exempt human subject research without obtaining prospective IRB approval.
- Implementing protocol modifications without obtaining prospective IRB approval.
- Altering from the informed consent process as described in the IRB-approved study application.
- Obtaining consent using an outdated consent form when the new consent form contained new information that may have caused the subject to change their mind about participating.
- Conducting research during a lapse in IRB approval.
- Not adhering to inclusion/exclusion criteria.
- Enrolling more subjects than were approved in the protocol of a greater than minimal risk study.
- Failure on the part of HRP staff involved in research review or oversight to abide by applicable laws or regulations, or HRP policies

What needs to be reported? (OHRP's Venn Diagram)



Under 45 CFR part 46: Do not report A; Report B and C.

Does an AE meet the definition of UAP?



What about deviations and non-reportable non-compliance?

Deviations and non-compliance that don't meet the reporting requirements should be logged by study team

MANDATORY:

- Greater than minimal risk studies
- Studies that meet the federal definition of a "clinical trial"
- If otherwise required by funding agency

Strongly recommended for all other studies
Not required to be submitted with annual review
Must be available upon request

Examples of non-reportable non-compliance/deviations

- Obtaining consent using an outdated consent form when there were no substantive differences between the consent form that was used and the consent form that should have been used (i.e., dates in the footer);
- Protocol deviations that do NOT adversely affect the safety, rights or welfare of human subjects or significantly compromise the quality or integrity of the research data;
- Subject Non-compliance that does not involve risk or compromise the quality or integrity of the research data;
- Performing non-safety related research procedures outside the protocol specified window (i.e., involuntarily administering a questionnaire outside of the protocol specified window)

Reporting Timelines: Adverse Events (AE)

External Adverse Event:

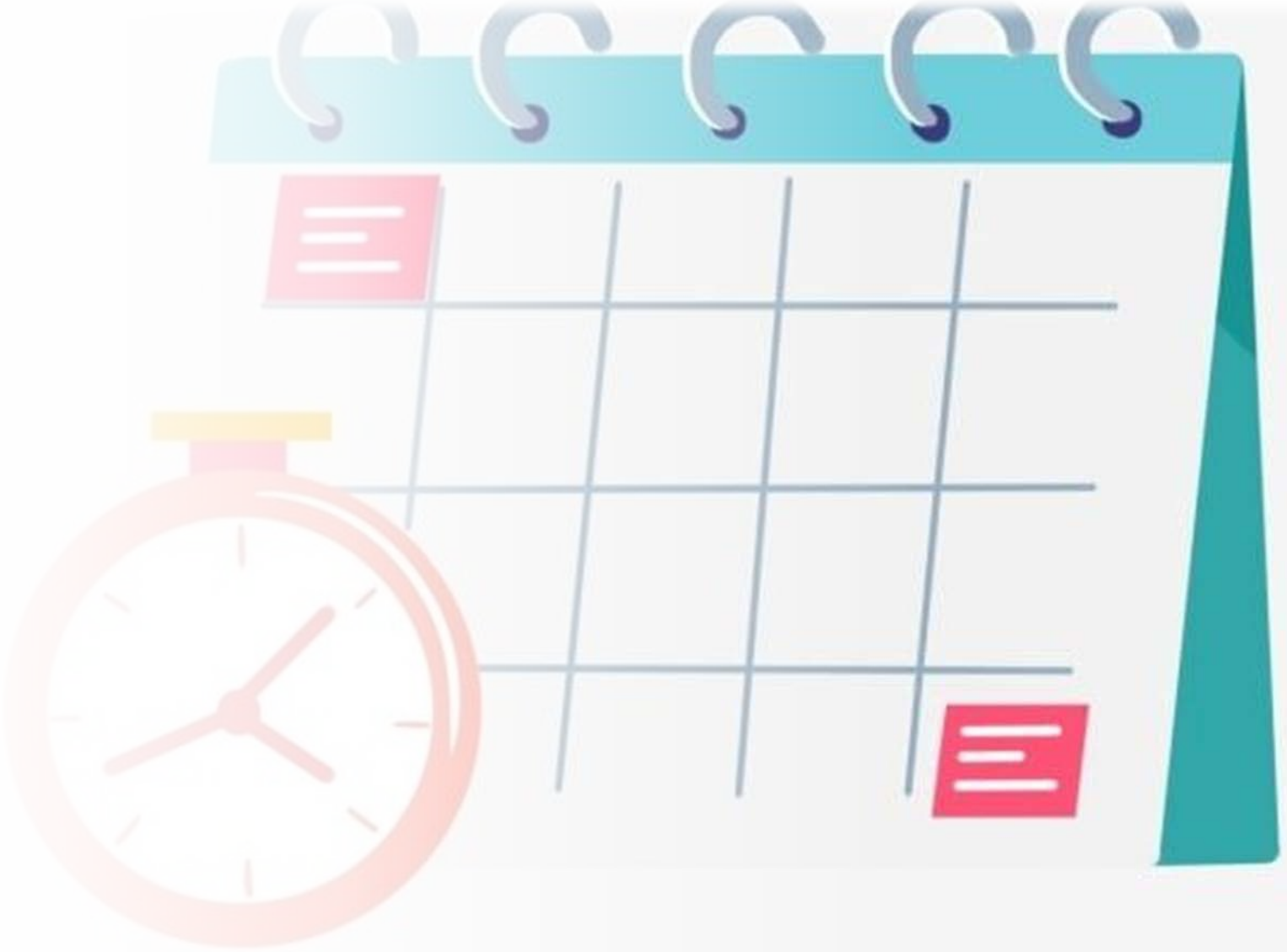
- Within **30 working days** of receipt: External AEs which are unexpected, serious and related to the research intervention
- AEs occurring in subjects enrolled in a multi-site study should be submitted to a monitoring entity
- May be placed on a convened IRB agenda for review
- IRB may act with regard to the local study in response to the AE e.g., suspend the local study enrollment, but will not report the event to a federal agency or sponsor unless required by the local action)

Internal Adverse Event:

- Within **24 hours** of learning of the event: Unexpected, fatal, or life-threatening, and related or possibly related to the research intervention
- Within **10 working days** of the investigator learning of the event: All other internal adverse events that meet the definition of an unanticipated problem involving risk to human subjects or others

Reporting Requirements for UAP and Reportable Non-Compliance

Unanticipated problems involving risks to human subjects or others and incidents of reportable non-compliance must be reported within **10 working days** of becoming aware of the information



Reportable New Information

PittPRO | Pitt Protocol Review Online

1. **RNI short title:** (uniquely identify this new information report)

participant death

2. * **Date you became aware of the information:**

6/7/18

All reportable events must be submitted through the RNI process in PittPRO

3. **Identify the categories that represent the new information:** (check all that apply)

Risk: Information that indicates a new or increased risk, or a safety issue. For example:

a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.

b. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or to describe a new risk.

☐ c. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.

d. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.

e. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.

f. Any changes significantly affecting the conduct of the research.

Harm: Any harm experienced by a subject or other individual that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures.

- ☐ **a.** A harm is "**unexpected**" when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.

- ☐ **b.** A harm is "**probably related**" to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.

- ☐ **Non-compliance:** Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
- ☐ **Audit:** Audit, inspection, or inquiry by a federal agency.
- ☐ **Report:** Written reports of study monitors.
- ☐ **Researcher error:** Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- ☐ **Confidentiality:** Breach of confidentiality.
- ☐ **Unreviewed change:** Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- ☐ **Incarceration:** Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- ☐ **Complaint:** Complaint of a subject that cannot be resolved by the research team.
- ☐ **Suspension:** Premature suspension or termination of the research by the sponsor, investigator, or institution.
- ☐ **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.

Important! Information that does not fit into one of the categories above does not need to be reported to the IRB as new information.

4. * **Briefly describe the problem or new information (data of occurrence or discovery, timeline, cause, action taken, changes made):**

We obtained additional information from the participant's wife. He apparently developed chest pains and passed out at home and DOA to Westmoreland ED. I am reporting this event as possibly related since no autopsy was performed and I cannot rule a relationship to the study drug.

5. **What actions need to be taken, or what changes are proposed to protect research subjects or others?**

I contacted the study sponsor and the DSMB and awaiting a decision as to whether the consent form will need revision or any changes to the drug administration.

6. **In the submitter's opinion:**

a. * **Does this information indicate a new or increased risk, or a safety issue?**

● **Yes** ○ No

b. * **Does the study need revision?**

○ Yes ● **No**

c. * **Does the consent document need revision?**

○ Yes ● **No**

ℹ If revisions are required, describe them above and submit a study modification for review.

7. **Related studies and modifications:**

ID	Short Title	Investigator	State	IRB Office
STUDY18030033	Black Simple Study	Rebecca Simms (pi)	Approved	Pitt IRB

8. **Attach files containing supporting information:**

Name

There are no items to display

What happens at the IRB: AE that is UAP

- Regulatory Affairs Specialist receives information
  - Requests additional info if needed
  - IRB Chair notified if immediate action for subject safety needs to be taken
  - Assigned to next convened meeting with expertise

What happens at the IRB: UAP Involving Risks to Subjects or Others & Reportable Non-Compliance

Regulatory Affairs Specialist & Chair review and make an initial determination

- Requests additional info if needed
- Refer to IRB Committee with appropriate expertise in certain circumstances
  - Compliance issues are typically assigned to the Executive Committee
- No further action required

Determinations:

- Confirm UAP Involving Risk to Human Subjects or Others
- Serious non-compliance, and/or
- Continuing non-compliance

Possible Committee Actions

Investigate:

- Request additional info about event & outcome
- Interview research staff
- Interview others
- Request audit

Terminate or Suspend (IRB will consider rights & welfare of subjects):

- Transfer subjects to another study
- Make arrangements for clinical care
- Allow continuation of some activities
- Require follow-up of subjects for safety
- Require outcomes to be reported
- Notify current and former subjects of the decision to terminate

Implement Administrative Action:

- IRB Chair or designee meet with PI, Staff, and/or dept chair
- Request Corrective Action Plan
- Require training & education
- Notify other interested entities (e.g. legal, risk management, privacy office)
- Suspend research privileges

Require other further actions as committee determines appropriate

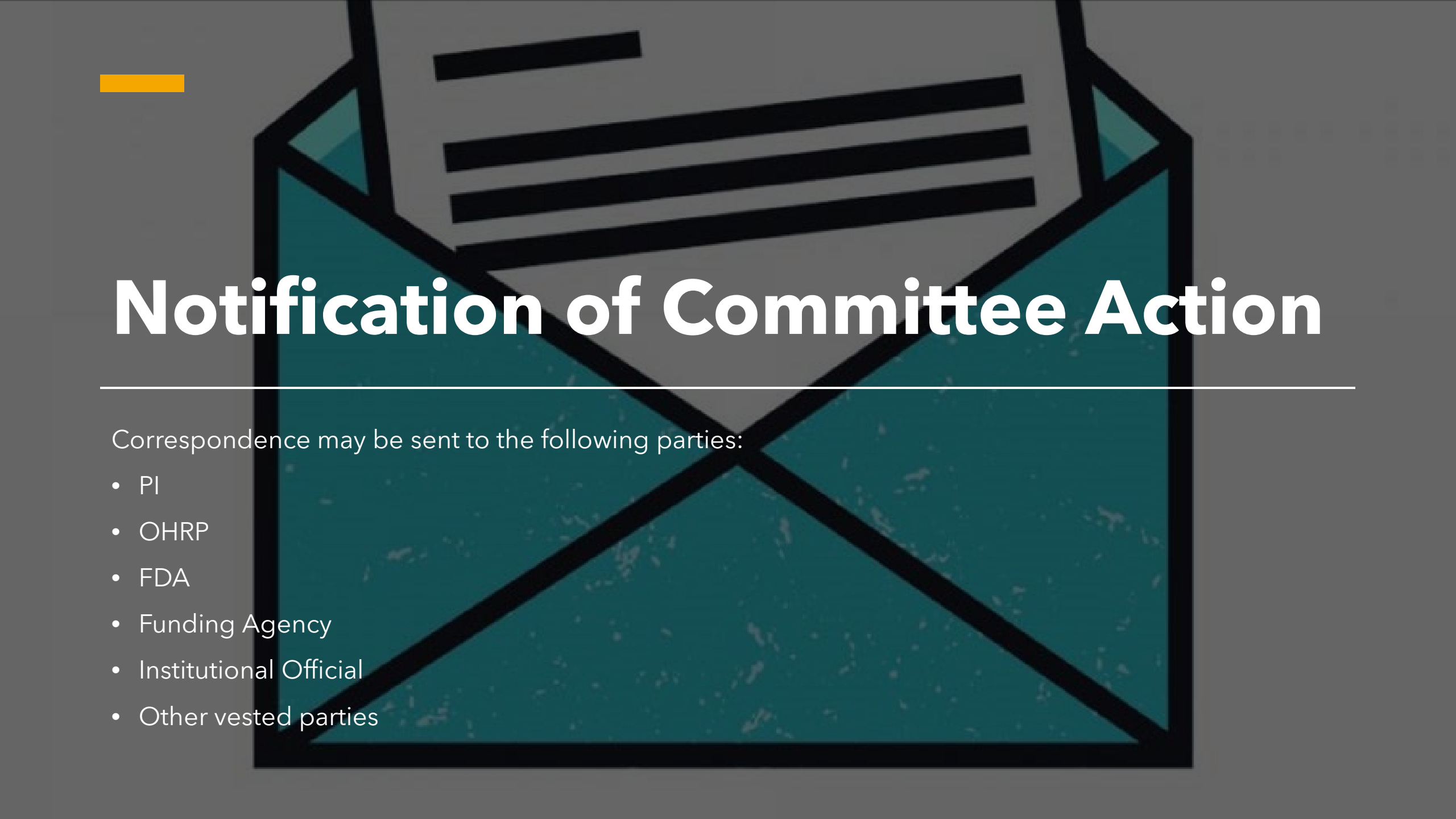
Require Modifications:

- Notification of subjects
- Performance of follow-up procedures
- Revise timeframe for continuing review

Require no further action

Possible Committee Actions

Investigate: • Request additional info about event & outcome • Interview research staff • Interview others • Request audit	**Implement Administrative Action:** • IRB Chair or designee meet with PI, Staff, and/or dept chair • Request Corrective Action Plan • Require training & education • Notify other interested entities (e.g. legal, risk management, privacy office) • Suspend research privileges	**Require Modifications:** • Notification of subjects • Performance of follow-up procedures • Revise timeframe for continuing review
Terminate or Suspend (IRB will consider rights & welfare of subjects): • Transfer subjects to another study • Make arrangements for clinical care • Allow continuation of some activities • Require follow-up of subjects for safety • Require outcomes to be reported • Notify current and former subjects of the decision to terminate	Require other further actions as committee determines appropriate	Require no further action



Notification of Committee Action

Correspondence may be sent to the following parties:

- PI
- OHRP
- FDA
- Funding Agency
- Institutional Official
- Other vested parties

Information resources

- IRB Policies and Procedures Chapter 17
- A-Z Guidance
  - RNI FAQs
  - Adverse Events/UAP Log
- OHRP Guidance: Unanticipated Problems Involving Risks & Adverse Events
- FDA Guidance: Adverse Event Reporting to IRBs – Improving Human Subject Protection