INSTRUCTIONS FOR REPORTING
UNANTICIPATED ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

1. For CUNY Central Offices projects or Research Foundation Central Office projects, please indicate “CUNY Central Office” or “RF Central Office” in the space for CUNY College and submit this form through IRBManager to the CUNY Office of Research Conduct. If you need help, call 212.794.5504.


3. DEFINITIONS
   a. **Adverse Event:**
      An adverse event is any untoward physical, psychological or social occurrence affecting subjects during the course of research. Adverse events occur most commonly in the context of biomedical research, although on occasion, adverse events can occur in the context of social and behavioral research.

   b. **Internal Adverse Events:**
      Internal adverse events are those experienced by subjects enrolled at the site(s) under the IRB’s jurisdiction for either multi-center or single-center research projects.

   c. **External Adverse Events:**
      External adverse events are those experienced by subjects enrolled in multi-center clinical trials at sites other than the site(s) over which the IRB has jurisdiction.

   d. **Unanticipated Problems:**
Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

1. 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;

2. related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests 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.

4. MANDATORY REPORTING TO THE IRB

The Principal Investigator must report any serious problem, adverse event, or outcome that occurs with frequency or degree of severity greater than that anticipated within 10 business days. In addition, the Principal Investigator must report any event or series of events that prompt the temporary or permanent suspension of a research project involving human subjects.

5. UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Federal regulations require procedures for the prompt reporting of unanticipated problems involving risks to subjects or others (referred to as “unanticipated problems”). Unanticipated problems include those events that

1. are not expected given the nature of the research procedures and the subject population being studied; and

2. suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized.

Not all unanticipated problems involve direct harm to subjects. Events can occur which are unexpected and result in new circumstances that increase the risk of harm to subjects without directly harming them. In addition, the event may have presented unanticipated risks to others (such as, the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects. In each case, while the event may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported. Such unanticipated problems could include:

- Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Any deviation from the protocol (protocol violation) that are related to participant safety, significant new findings, a defined subset of adverse events and IND safety reports
- 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
- Any compliant from a participant that indicates an unanticipated risk or which cannot be resolved by the research staff
- Breach of confidentiality of research data
- Breach of privacy/confidentiality/data security/loss of study data/destruction of study data due to noncompliance
- Incorrect labeling/dosing of study medication or test article
- Any event that requires prompt reporting according to the sponsor

Adverse Events

An adverse event is any untoward physical, psychological or social occurrence affecting subjects during the course of research. Adverse events occur most commonly in the context of biomedical
research, although on occasion, adverse events can occur in the context of social and behavioral research.

Adverse events may be serious or not serious. A serious adverse event is one that is fatal or life-threatening, requires or prolonged hospitalization, produces a disability, or results in a congenital anomaly/birth defect. In social and behavioral research, a serious adverse event is one that results in severe emotional trauma, results in loss of employment or income, or requires counseling or therapy.

Adverse events may be expected or unexpected. An unexpected adverse event is an adverse event not previously known or anticipated to result from:

(a) the interventions and interactions used in the research;
(b) the collection of identifiable private information under the research;
(c) an underlying disease, disorder, or condition of the human subject; and/or
(d) other circumstances related to the research or an underlying disease, disorder, or condition of the subject.

An assessment of the significance and expectedness of a particular adverse event or group of adverse events also needs to account for the level of severity and frequency of the adverse events occurring in the subject population.

Adverse events may be internal or external. Internal adverse events are those experienced by subjects enrolled at the site(s) under the IRB’s jurisdiction for either multi-center or single-center research projects. External adverse events are those experienced by subjects enrolled in multi-center clinical trials at sites other than the site(s) over which the IRB has jurisdiction.

Relating Adverse Events to Unanticipated Problems

Not all adverse events would be considered unanticipated problems. Many adverse events, both serious and non-serious, occurring in the context of research are expected in light of the known untoward effects of the research procedures or are due to the natural history of subjects’ underlying diseases and conditions. Therefore, these adverse events do not represent unanticipated problems, and thus would not need to be reported.

Three categories of adverse events would be considered unanticipated problems and would require reporting:

1) Adverse events that are serious, unexpected, and related or possibly related to participation in the research.

2) Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.

3) Other unexpected adverse events, regardless of severity, that may alter the IRB’s analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that must be reported under HHS regulations at 45 CFR 46.
Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem

An adverse event occurs in one or more subjects.
One or more adverse events occur.

1. Is the adverse event unexpected in nature, severity, or frequency?

   YES

   2. Is the adverse event related or possibly related to participation in the research?

      NO

      YES

      3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? NOTE: If the adverse event is serious, the answer is always “YES.”

         YES

         Report the adverse event as an unanticipated problem under 45 CFR part 46

         NO

         The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46
As was stated above, not all unanticipated problems involve adverse events since the problem may not involve direct harm to the subjects and still increase the risk to subjects or others.

6. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

REPORTING

All events which may be considered unanticipated problems involving risk to subjects or others must be reported to the IRB. As previously noted, because most individual adverse events do not appear to represent unanticipated problems, the vast majority of reports of adverse events do not need to be submitted to the IRB.

Only those adverse events which are considered unanticipated problems must be reported to the IRB. See above for the categories of adverse events that would be considered unanticipated problems. Investigators must maintain a record of all reported adverse events which are not considered unanticipated problems and submit a summary at the time of continuing review.

The PI reports adverse events to the IRB on the Adverse Event and Unanticipated Problem Report Form. The IRB notifies the Office of Research Conduct in a timely manner of the report by submitting the original signed copy of the adverse event report to the Office of Research Conduct for review and approval.

Internal Adverse Events

The Principal Investigator assesses whether the adverse event may be considered an unanticipated problem based on the criteria presented above.

1) If the Principal Investigator determines that the adverse event may be considered an unanticipated problem, the Principal Investigator reports it to the IRB within 10 working days using the Adverse Event and Unanticipated Problem Report Form. The report shall include the following information:

   (a) Appropriate identifying information, such as (i) the title of the research protocol; (ii) the Investigator’s name; (iii) the IRB protocol number; (iv) the name of the supporting agency and the relevant award number; and (v) any relevant investigational new drug (IND) or investigational device exemption (IDE) number.

   (b) A complete, detailed description of the external adverse event and the basis for determining that it may be considered an unanticipated problem.

   (c) A description of any actions that have been taken or proposed by the study sponsor, the study coordinating site, any other monitoring entity (for example, a Data Safety Monitoring Board (DSMB)), and/or the local Principal Investigator in response to the unanticipated problem (such as, suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent information and/or process).

   For multi-center research, the local Principal Investigator should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents being proposed by the local Investigator. The Principal Investigator also must ensure that the adverse event is reported to a central or independent monitoring entity (such as, a DSMB, an independent medical monitor, coordinating site, and/or sponsor) if required under a monitoring plan described in the IRB-approved protocol.

2) If the Principal Investigator determines that the adverse event is not considered an unanticipated problem, the Principal Investigator only needs to ensure that the adverse event is reported to a central or independent monitoring entity (such as, a DSMB, an independent medical monitor, coordinating or statistical center, and/or study sponsor) if required under the monitoring plan described in the IRB-approved protocol. If the monitoring entity subsequently determines, in contrast to the Investigator’s determination, that the adverse event does represent an unanticipated problem, procedures should be in place for the monitoring entity to communicate this determination to the Investigator, who then should report the unanticipated problem to the IRB, following the procedures outlined below for external adverse events.
Internal adverse events that are **unexpected, fatal or life-threatening**, and related to the research intervention **must be reported to the IRB within 24 hours of the event**. Internal adverse events which are considered unanticipated problems (but not fatal or life threatening), shall be reported to the IRB within 10 working days of the investigator becoming aware of the event.

**External Adverse Events**

For reports of external adverse events from the study sponsor, a study coordinating or statistical center, a DSMB, or other central monitoring entity, the Principal Investigator only needs to submit to the IRB reports of events that have been determined, preferably by the central monitoring entity, to represent an unanticipated problem based on the criteria presented above.

1) If the Principal Investigator determines that the adverse event may be considered an unanticipated problem, the Principal Investigator reports it to the IRB using the Adverse Event and Unanticipated Problem Report Form as described for internal adverse events.

2) For any report of an external adverse event determined not to be considered an unanticipated problem, the Principal Investigator maintains a copy of the external adverse event report and documentation of the basis for this determination. This record is to be made available to the IRB or other authorized entities on request.

Reports of external adverse events submitted to the IRB should present the adverse event in the context of the entire multi-center study, if possible. In addition, the local Principal Investigator should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents independently proposed by the local Investigator.

External adverse events (that is, external sponsor generated safety reports) which are considered unanticipated problems shall be reported to the IRB **within 30 working days** of their receipt.

**Other Unanticipated Problems (not related to adverse events)**

Unanticipated problems not related to adverse events must be reported to the IRB **within 10 working days** of the event using the Adverse Event and Unanticipated Problem Report Form.
PART I: SERIOUS ADVERSE EVENT OR UNANTICIPATED PROBLEM INFORMATION
TO BE COMPLETED BY PRINCIPAL INVESTIGATOR

1. Describe in detail the nature of the adverse event or unanticipated problem and the timing of the event.

2. Describe this adverse event or unanticipated problem and its relation to the research participants or others.

3. Select type of adverse event or unanticipated problem. Select all that apply.
   - [ ] Adverse event that is serious, unexpected, and related or possibly related to participation in the research.
   - [ ] Serious adverse event that was expected in some subjects, but is determined to be occurring at a significantly higher frequency or severity than expected.
   - [ ] Internal adverse event
   - [ ] External adverse event
   - [ ] Other unexpected adverse event, regardless of severity, that may alter the IRB’s analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
   - [ ] Other unanticipated problem not related to adverse events

4. Select the option(s) that best describes the outcomes attributed to the adverse event or unanticipated problem. (Check all that apply and explain fully)
   - [ ] Breach of Confidentiality
   - [ ] Severe or Significant Emotional or Psychological Distress
   - [ ] Physical Injury
   - [ ] Immediate Medical Care Required
   - [ ] Death
   - [ ] Other, please specify.

5. Describe the corrective action taken. (Check all that apply and explain fully)
   - [ ] Stop Enrollment of New Participants
   - [ ] Change Data Management/Coding Procedures
   - [ ] Halt the Study
   - [ ] Change Recruitment Procedures
   - [ ] Review Procedures
   - [ ] Change Confidentiality and Privacy Protection Procedures
   - [ ] Staff Education and Training; please specify.
   - [ ] Other; please specify.
   - [ ] None; please explain.

6. Do you judge the event or problem to be a directly related to the research?
   - [ ] Yes
   - [ ] No
   Please explain.
7. Will the consent form be modified?
   [ ] Yes
   [ ] No
   Please explain.

8. Will the currently enrolled participants be re-consented?
   [ ] Yes
   [ ] No
   If yes, please explain the process for re-consenting.
   If no, please explain why re-consenting is not necessary.

9. Will current research participants be notified of the adverse event or unanticipated problem?
   [ ] Yes
   [ ] No
   Please explain.

   **PART II: PRINCIPAL INVESTIGATOR’S ORIGINAL SIGNATURE**

   By signing below, the Principal Investigator (and faculty advisor, if appropriate) assures the information contained in this form is true and accurate.

   | Principal Investigator Signature |
   | Date                          |
   | Faculty Advisor’s Signature  |
   | Date                          |
PART III: IRB CHAIR DETERMINATIONS

1. The adverse event or unanticipated problem appears to be:
   - [ ] Directly Related to the Research
   - [ ] Indirectly Related to the Research
   - [ ] Not Related to the Research

2. The adverse event or unanticipated problem requires modification of the following:
   - [ ] Protocol
   - [ ] Consent form
   - [ ] No modifications are required
   - [ ] Other; please specify.

3. Specify any modifications to the protocol, consent form or procedure, materials, etc., that the IRB requires to correct the problem. If none are required, explain why.

4. Required modifications must be attached to this form and submitted to the IRB Office for review in _____ days.

If any modifications are required, the Principal Investigator must make appropriate modifications and submit to the IRB for review. The IRB must send a copy to the Office of Research Conduct.

PART IV: PRELIMINARY DECISION

The IRB Chair will complete this section and forward it to the Executive Director of Research Conduct at the time the IRB notifies the Principal Investigator of required modifications.

1. IRB ACTION(S):
   - [ ] Require modification (attach correspondence to PI specifying requirements)
   - [ ] Allow research to continue
   - [ ] Suspend research
   - [ ] Other, please specify

2. IRB Chair Signature

3. Date
4. **EXECUTIVE DIRECTOR OF RESEARCH CONDUCT ACTION(S)**
   [ ] Require modification
   [ ] Allow research to continue
   [ ] Suspend research
   [ ] Other, please specify

5. Executive Director of Research Conduct Signature

6. Date

**PART V: FOLLOW-UP APPROVAL**

The IRB Chair will complete this section and forward it to the Executive Director of Research Conduct after the IRB receives and approves the required modifications.

1. **IRB ACTION(S):**
   [ ] Require modification (attach correspondence to PI specifying requirements)
   [ ] Allow research to continue
   [ ] Suspend research
   [ ] Other, please specify

2. IRB Chair Signature

3. Date

4. **EXECUTIVE DIRECTOR OF RESEARCH CONDUCT ACTION(S)**
   [ ] Require modification
   [ ] Allow research to continue
   [ ] Suspend research
   [ ] Other, please specify

5. Executive Director of Research Conduct Signature

6. Date

**PART VI: FINAL APPROVAL**

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