HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

Policy Number: 801
SOP Title: Reporting Research Events

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB Chairs, IRB Administrators, Protocol Navigators

Revision Approval: [Signature]
Deputy Director for Intramural Research

Implementation date: 7/1/2019
POLICY

1. PURPOSE
   1.1. This policy outlines the requirements for reporting research-related events to the Institutional Review Board (IRB).

2. SCOPE
   2.1. This policy applies to all NIH investigators conducting human subjects research (also referred to in this policy as “studies”) and to the Office of Human Subjects Protections (OHSRP).

   2.2. This policy applies to investigators not covered by the NIH Federalwide Assurance (FWA) when the NIH is the Reviewing IRB for human subjects research conducted by these investigators.

3. POLICY
   3.1. For all human subjects research in which an NIH IRB is the Reviewing IRB, NIH Principal Investigators (PIs) and, as applicable, non-NIH Site PIs/Lead Investigators (further referred to as non-NIH investigators), are required to ensure that all reportable events, as defined in this policy, are reported to the OHSRP office of Compliance and Training within the time frames as specified in this policy.

   3.1.1. The NIH Principal Investigators (PIs)/designee and, as applicable, non-NIH Investigators must report events to the OHSRP office of Compliance and Training via the Reportable Event Submission Form (REF) in NIH iRIS (further referred to as iRIS) in accordance with Section 5.1., whether the events occur at the NIH or a non-NIH site;

   3.2. For human subjects research when the Reviewing IRB is not an NIH IRB, NIH PIs/Lead investigators (further referred to as NIH PI(s) to include NIH PIs, NIH Site PIs in the case of multi-site research, and NIH AIs participating in a collaborative research protocol with a non-NIH PI) are required to ensure that the reporting requirements of the Reviewing IRB are followed by NIH staff.

   3.2.1. When the Reviewing IRB is a non-NIH IRB, and the event occurred at an NIH site, the NIH PI must report the event to the Reviewing IRB in accordance with that IRB’s instructions, and also to the OHSRP office of Compliance and Training
3.2.2. When the Reviewing IRB is a non-NIH IRB, and the event occurred at a non-NIH site, the NIH PI/Lead Investigator is required to ensure that the reporting requirements of the Reviewing IRB are followed. The investigator does not also report these events to the OHSRP office of Compliance and Training.

3.3. Additional reporting may also be required as specified by an NIH Institute/Center (IC) or other NIH policy.

3.4. This policy’s reporting requirements are in addition to the requirements of regulatory agencies (such as the FDA) and/or any institutionally agreed-upon requirements, e.g., with study sponsors or through reliance agreements.

4. DEFINITIONS

4.1. Adverse Event (AE) - Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in research, whether or not considered related to the subject’s participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

4.2. NIH Investigator - An NIH federal employee (intramural or extramural) who is conducting human subjects research on behalf of the NIH. Additionally, this designation includes an investigator who is not an NIH federal employee but who is conducting human subjects research while working at an NIH site with an NIH employee. These researchers may include Guest Researchers, Special Volunteers, contractors (subject to the terms of the contract), Intramural Research and Cancer Research Training Awardees and colleagues from academia and industry who are not Special Government Employees (SGEs) or Intergovernmental Personnel Act appointees.

4.3. Non-Compliance - Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not.

4.3.1. Serious non-compliance - Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.
4.3.2. **Continuing non-compliance** - A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non-compliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

4.4. **Protocol Deviation (PD)** - Any change, divergence, or departure from the IRB-approved research protocol.

4.4.1. **Major Deviations** - Deviations from the IRB-approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.

4.4.2. **Minor Deviations** - Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

4.5. **Reportable Event** - An event that occurs during the course of human subjects research that requires notification to the IRB. For the purposes of this policy, reportable events include non-compliance and unanticipated problems involving risks to subjects or others (also referred to as UPs), major deviations, deaths related or possibly related to research activities and new information that might affect the willingness of subjects to enroll or continue participation in the study.

4.6. **Reviewing IRB** - The IRB responsible for reviewing human subjects research and determining that the research meets the required criteria for approval under the HHS regulatory requirements at 45 CFR 46 and, as applicable, the pertinent Subparts of 21 CFR.

4.7. **Serious Adverse Event (SAE)** - is any Adverse Event that:
- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; OR
• Based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In terms of IND safety reporting, this term is used synonymously with serious suspected adverse reaction. (See 21 CFR 312.32(a) for the FDA definition.)

4.8. Unanticipated (Unexpected) - An experience that was not expected or previously observed, or is not consistent in nature, severity, or frequency with existing risk information, such as in the investigator’s brochure, device manual, research protocol, consent form, or other available information (e.g., IND application for an investigational drug or IDE application for an investigational device). Interchangeable with “unexpected”. This includes an event or problem occurring in one or more subjects in a research study that is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the event/problem.

4.9. Unanticipated Adverse Device Effect - means 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.

4.10. Unanticipated Problem Involving Risks to Subjects or Others (UP) - Any incident, experience, or outcome that meets all the following criteria:

4.10.1. 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; and

4.10.2. Related or possibly related to participation in the research (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

4.10.3. Suggests that the research places subjects, or others (which may include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological,
economic, or social harm) related to the research than was previously known or expected.

5. RESPONSIBILITIES AND REQUIREMENTS

5.1. Responsibilities of investigators:

5.1.1. The PI must ensure that all AEs and SAEs are appropriately identified, tracked and recorded, according to the IRB-approved protocol, data and safety monitoring plan, and in accordance with any additional NIH, regulatory, IC-specific and/or study sponsor requirements. (Policy 506 Data and Safety Monitoring)

5.1.2. The NIH PI/designee and, as applicable, non-NIH Investigators, must ensure that the following events are reported to the NIH IRB within the time frames specified below. (See Appendix 1: Investigator Reporting Requirements and Timeframes for tabular view of these requirements)

5.1.2.1. Non-compliance: Any actual or suspected non-compliance by any investigator or entity associated with the protocol must be reported by the NIH PI/designee within 7 calendar days of any investigator or individual associated with the protocol first becoming aware, unless otherwise indicated in this policy. Please refer to policy 802 Non-compliance in Human Subjects Research.

5.1.2.1.1. Non-NIH IRB Determinations of serious and/or continuing non-compliance about an NIH investigator: If the NIH is relying on a non-NIH IRB and the Reviewing IRB makes a determination of serious and/or continuing non-compliance regarding an NIH investigator, then, even if the determination has already been provided to OHSRP either directly or via the NIH Institutional Official (IO)/designee, the NIH PI/designee must report this in iRIS within 7 calendar days of any member of the research team being notified of the determination by the Reviewing IRB. The NIH PI must provide the OHSRP office of Compliance and Training with documentation from the Reviewing IRB unless this documentation has already been provided directly to the office by the Reviewing IRB or via the IO.
5.1.2.2. **Major Deviation:** A deviation must be reported within 7 calendar days of an investigator becoming aware of an actual or suspected deviation. Although protocol deviations are also non-compliance, these should only be reported once as deviations.

5.1.2.3. **Unanticipated Problem (UP):** A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP.

5.1.2.4. **Death:** Any death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of an investigator becoming aware of the death.

5.1.2.5. **New information that might affect the willingness of a subject to enroll or remain in the study:** Should be reported within 7 calendar days of an investigator first becoming aware.

5.1.2.6. **Any suspension or termination of research activities:** Including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency must be reported within 7 calendar days of an investigator becoming aware.

5.1.2.7. **Investigators must provide the following information to the IRB in summary format:** At the time of continuing review, or when otherwise specifically requested by the IRB or the OHSRP office of Compliance and Training. Investigators should provide a high-level summary of these events that have occurred since the time of the last IRB review and not a line item listing:

- Major and minor protocol deviations.
- Noncompliance reported to the IRB that is not related to a protocol deviation.
- Adverse Events and Serious Adverse Events that do not meet the definition of an UP.
- UPs reported to the IRB.

5.1.3. **For FDA regulated studies,** investigators are required to report events to the study sponsor as described in the protocol and to immediately (i.e., no longer than 10 days) report SAEs or UADEs to the study sponsor and, if also an actual or
suspected UP, to the IRB within 7 calendar days of an investigator becoming aware.

5.2. Responsibilities of the OHSRP Office of Compliance and Training and the IRB(s):

5.2.1. When NIH is the Reviewing IRB, the OHSRP office of Compliance and Training is responsible for the following:

5.2.1.1. Conducting initial evaluation and triage of all reportable events submitted using iRIS.

5.2.1.2. In consultation, as needed, with the OHSRP Director, IRBO Director, and/or Executive Chair, determining if any reported event requires immediate action to protect the rights, safety or welfare of research subjects and if so, communicating such actions to the PI and the IRB.

5.2.1.3. Referring potentially serious and/or continuing non-compliance to the Research Compliance Review Committee (RCRC).

5.2.1.4. Referring reported UPs to the convened IRB for determination and review of any proposed changes to the protocol or consent made by the PI in response to the UP.

5.2.1.5. Reporting to OHRP and, as applicable, FDA, all NIH IRB determinations of serious and/or continuing non-compliance, UPs, or NIH IRB suspensions or terminations of IRB approval within 30 days of the determination, suspension or termination of IRB approval. The Office may make interim reports in advance of the IRB’s final determination as deemed necessary.

5.2.2. When NIH is the Reviewing IRB, the RCRC, as a duly constituted IRB, is responsible for the following:

Reviewing possible serious and/or continuing non-compliance occurring within studies under the NIH IRB’s purview.

Determining whether serious and/or continuing non-compliance occurred and evaluating the adequacy of any proposed corrective action. (See Policy 802 Non-compliance in Human Subjects Research).
5.2.3. For studies in which the Reviewing IRB is a non-NIH IRB, the regulatory responsibility for reporting to federal agencies lies with the Reviewing IRB unless otherwise specified in the reliance agreement.

6. REFERENCES

6.1. Federal Regulations

HHS: 45 CFR 46
FDA: 21 CFR parts 50, 56, 312 and 812

6.2. NIH Policies

Policy 506 Data and Safety Monitoring
Policy 802 Non-Compliance in Human Subjects Research

6.3. Guidance

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1): Guidance for Industry

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others (2007)

7. APPENDICES:

7.1. Appendix 1: Investigator Reporting Requirements and Timeframes

8. REVISION HISTORY: N/A

9. SUPERSEDES DATE: 07/01/2019, SOP 16 REPORTING REQUIREMENTS FOR UNANTICIPATED PROBLEMS, ADVERSE EVENTS AND PROTOCOL DEVIATIONS

V.4 dated 3/14/2016
V.3 dated 2/24/2016
V.4 dated 2/26/14 (form only, note out of order versioning)
V.2 dated 10/01/2013 (form only)
V.1 dated 6/11/2013
<table>
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<tr>
<th>Investigator status</th>
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<th>Non-NIH IRB is Reviewing IRB</th>
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| NIH PI, or as applicable, the NIH lead site investigator | • Report the following events to the NIH IRB within 7 calendar days of any investigator first becoming aware*  
  ➢ Actual or suspected non-compliance  
  ➢ Actual or suspected major deviations  
  ➢ Actual or suspected Unanticipated Problems (UPs)  
  ➢ New information that might affect the willingness of a subject to enroll or remain in the study  
  ➢ Suspension or termination of research activities, including holds on new enrollment, placed upon the research by the study sponsor, NIH or IC leadership, or any regulatory agency  
  • Death of a research subject that is possibly, probably or definitely related to the research must be reported within 24 hours of the investigator becoming aware of the death.  
  • For FDA regulated studies, report events to the study sponsor as described in the protocol and immediately report (i.e., no longer than 10 days) SAEs or UADEs to the study sponsor and, if also an actual or suspected UP, to the IRB within 7 calendar days of the investigator becoming aware.  
  • At the time of CR, submit a high-level summary (not a line item | • Report events to the Reviewing IRB as per its policy  
  • If event occurs at an NIH site, also report to the OHSRP office of Compliance and Training within 7 calendar days*  
  • For FDA regulated studies, report events to the study sponsor as described in the protocol and immediately report (i.e., no longer than 10 days) SAEs or UADEs to the study sponsor and, if also a UP, to the IRB within 7 calendar days.  
  • Report any determinations by the non-NIH Reviewing IRB of serious and/or continuing non-compliance by an NIH investigator in iRIS within 7 calendar days.* Also, provide the OHSRP office of Compliance and Training with documentation from the Reviewing IRB unless |
listing) of events including: major and minor protocol deviations; noncompliance reported to the IRB that is not related to a protocol deviation; Adverse Events and Serious Adverse Events that do not meet the definition of an UP; and UPS reported to the IRB.

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<td>Non-NIH Investigator</td>
<td>Requirements for reporting events to the NIH IRB are the same as those for the NIH investigators as defined above** (Non-NIH investigators should consult their institution’s policies if local reporting is also required.)</td>
<td>Report events to the Reviewing IRB as per its policy</td>
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*Submit a Reportable Event Form in iRIS

** Mode of submission by the Non-NIH Investigator will be determined by the IRBO