

8.1 Review of Adverse Events and Adverse Device Effects

1.0 Purpose

The purpose of this policy is to describe the process for reporting research related Adverse Events (AEs) and Adverse Device Effects (ADEs) to the ORA and the IRB, and the process for review of AEs and ADEs.

2.0 Policy

It is the policy of the Organization that:

- 2.1. Internal AEs must be promptly reported to the ORA if the PI determines that the AE is unexpected, AND related to, or possibly related to, the research intervention or procedures.
 - 2.2. Internal UADEs must be reported to the ORA if the PI determines that the ADE is unexpected AND related to (caused by or associated with) the device.
 - 2.3. External AEs must be reported to the ORA if the PI determines that the external AE is unexpected AND related or possibly related to the research intervention or procedure AND serious AND the external AE requires a change to the protocol and/or informed consent form and/or re-consent of subjects.
 - 2.4. The ORA and the IRB will comply with requirements of 21 CFR 312 and 21 CFR 812 as applicable.
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3.0 Definitions

- 3.1. Adverse Event (AE) is defined as any untoward or unfavorable occurrence in a human subject temporally associated with the subject's participation in the research (whether or not related to participation in the research). An AE may be expected or unexpected, and related or unrelated to the subject's participation in the research. This policy does not make a differentiation between medical and non-medical AEs. AEs occurring in the context of an FDA regulated clinical investigation are defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)).
 - 3.1.1. Unexpected AE: An AE in which the specificity, severity, or frequency is not consistent with (a) the IRB application and detailed protocol; (b) Risk information in

the ICF; or (c) the current investigator's brochure or similar materials.

- 3.1.2. Related AE: An AE which there is clear causality, or a strong temporal relationship with the research intervention or procedure.
 - 3.1.3. Possibly Related AE: An AE which may have been caused by the research intervention or procedure, but there is insufficient information attribute clear causality. An attribution as "possibly related" requires less certainty than "related"; however, there must still be evidence suggesting such a causal relationship (for example, temporal relationship to the intervention, known pharmacological property of drug, exclusion of other causes).
 - 3.1.4. Serious AE: An AE which results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Events may also be considered serious when they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (21 CFR 312.32(a)).
 - 3.2. Adverse Device Effect (ADE) is defined as an adverse effect caused by, or associated with, use of a medical device in a clinical investigation.
 - 3.2.1. Unanticipated Adverse Device Effect (UADE): 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 (per 21 CFR 812.3(s)).

Note: The FDA device regulations at 21 CFR 812.3(s) define an adverse device effect which is different than the definition of an adverse event in FDA IND regulations at 21 CFR 312.32(a). Significantly, an AE may be expected or unexpected, related or unrelated, or serious or not serious. An UADE is related (caused by or associated with) and unexpected (not previously identified).
 - 3.2.2. Serious UADE: An UADE which results in any of the outcomes as described above for serious AEs, or one in which required intervention to prevent permanent impairment or damage.
 - 3.3. Internal AE or UADE: An AE/UADE experienced by a subject in a study conducted at the Organization or at an external site under the jurisdiction of the UNMC IRB.
 - 3.4. External AE or UADE: An AE/UADE experienced by a subject in a study conducted at an external site (a site not under the jurisdiction of the UNMC IRB).
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4.0 Investigator Responsibilities

- 4.1. Internal AEs and UADEs
 - 4.1.1. Internal AEs must be promptly reported to the ORA if the PI determines that the AE is unexpected, AND related to, or possibly related to, the research intervention or procedures. Internal AEs meeting the above conditions must be reported no later than two business days following PI notification that the event occurred, or within 24 hours if the internal AE is fatal.
 - 4.1.1.1. Except for congenital anomalies or birth defects, and cancer, internal AEs occurring more than 90 days after the subject has completed study

interventions are generally considered unrelated and are therefore not reportable.

- 4.1.2 Internal UADEs must be reported to the ORA if the PI determines that the ADE is unexpected AND related to (caused by or associated with) the device. Internal ADEs meeting the above conditions must be reported no later than two business days following PI notification that the event occurred, or within 24 hours if the internal ADE is fatal.
 - 4.1.2.1. Internal ADEs meeting the above conditions must be reported for as long as the device is classified as investigational.
- 4.1.3. Internal AEs that occur on studies for which the Organization is relying on another IRB must be reported to the ORA if the PI determines that the AE is unexpected, AND related to, or possibly related to, the research intervention or procedures.
 - 4.1.3.1. Internal AEs that occur on studies for which the Organization is relying on another IRB must also be reported to that IRB in accordance with the reliance agreement.
- 4.2. External AEs
 - 4.2.1. External AEs must be reported to the ORA if the PI determines that the external AE is unexpected AND related or possibly related to the research intervention or procedure AND serious AND the external AE requires a change to the protocol and informed consent form and re-consent of subjects. External AEs meeting the above conditions must be reported no later than five business days following PI notification that the event occurred.
 - 4.2.2. The PI is responsible for keeping up-to-date on all information which impacts risk(s) or subject safety and submitting to the IRB changes in the protocol and the ICF as necessary.
 - 4.2.3. The IRB will not accept, acknowledge or review external safety reports if there are no changes required in the protocol, IRB application and/or ICF.
- 4.3. External UADEs
 - 4.3.1. External UADEs which occur at other institutions must be reported to the UNMC IRB no later than five business days following PI notification from the sponsor that the event occurred) in accordance the requirements of 21 CFR 812.150(b)(1).
 - 4.3.2. Once the status of a study is changed to “completed”, the IRB will no longer accept external UADE reports except under circumstances where the report involves important new risk information.

5.0 ORA Responsibilities

- 5.1. AEs reported to the ORA will be reviewed by the an IRB Analyst, in consultation with the Executive chair or designee to determine if the AE satisfies the criteria for reporting per section 4.1.1 (unexpected, and related to, or possibly related to, the research) or the event is a UADE (related and unexpected).
 - 5.2. The IRB Executive Chair/designee will take all actions necessary to protect human subjects in accordance with HRPP policy 8.6 (Study Hold, Suspension, and Termination).
 - 5.3. All internal AEs which satisfy the criteria for reporting per section 4.1.1, and all internal or external UADEs will be referred to the convened IRB.
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6.0 IRB Responsibilities

- 6.1. The convened IRB will review reports of AEs and UADEs in accordance with HRPP policy 2.2 (Full IRB Review).
 - 6.2. To approve the AE or UADE report, the IRB must ensure the following criteria are met:
 - 6.2.1. The risk/benefit relationship of the research remains acceptable.
 - 6.2.2. No additional changes in protocol are necessary to further minimize risk.
 - 6.2.3. No additional monitoring of data is necessary to ensure the safety of subjects.
 - 6.2.4. The consent document(s) as written/revised are acceptable.
 - 6.2.5. Currently enrolled subjects will be provided new information related to the AE per requirements at 45 CFR 46.116(c)(5) and/or 21 CFR 50.25(b)(5).
 - 6.3. The IRB must determine whether
 - 6.3.1. Re-consent must be obtained from currently enrolled subjects, and, if so, how soon such re-consent must occur.
 - 6.3.2. Currently enrolled subjects may continue on study.
 - 6.3.3. Further subject accrual is permitted.
 - 6.3.4. Additional information must be provided to past subjects.
 - 6.3.5. The current continuing review schedule is appropriate.
 - 6.4. The IRB must determine if the AE/UADE is an Unanticipated Problem in accordance with HRPP policy 8.3 (IRB Review of Unanticipated Problems Involving Risk to the Subject or Others).
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7.0 Reporting AEs/UADEs to Institutional Officials, OHRP, FDA, and Department or Agency Heads

All required reports will be submitted in accordance with HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

DOCUMENT HISTORY:

? Written: 1/18/2016 (Approved: 1/18/2016) - original author not recorded

? Revised: 11/27/2017 - revision not documented

? Revised: 5/4/2023 - Clarified investigator responsibilities for reporting AEs that occur on studies for which the Organization is relying on another IRB; deleted expectation that reportable external AEs be followed by change request (since such AE reports often are made in the context of a change request) (section 4.2.1); stylistic changes.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

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