Section 8: AEs, Unanticipated Problems and Compliance

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.

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).

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.

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).

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).

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? 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)}

8.2 Review of Study Related Complaints

1.0 Purpose

The purpose of this policy is to describe the process for reporting research related complaints to the ORA and the IRB, and the process for review of complaints.

- 1.1. For the purposes of this policy “complaints” includes problems, concerns, or questions raised by current, prospective, or past research participants or their representatives regarding their participation in human subject research. Complaints by research personnel or other interested parties regarding the functioning of one or more components of the HRPP will be addressed as per HRPP Policies 1.22 (Assessment of the HRPP) and/or HRPP Policy 8.5 (Noncompliance by the IRB or Other Components of the HRPP).

2.0 Policy

It is the policy of the Organization that:

- 2.1. Complaints involving the human research protection program be promptly reported to the ORA and to the IRB.
- 2.2. Complaints under the jurisdiction of the IRB will be investigated and resolved as appropriate and reported to Organizational officials.
- 2.3. Findings of serious or continuing noncompliance and suspensions or terminations of IRB approval as a result of a complaint will be promptly reported to OHRP, FDA and sponsors or funding agency heads in accordance with HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

3.0 Complainant (or Other Reporters’) Responsibilities

- 3.1. Complaints from current, prospective, or past research participants or their representatives may be received by the Principal Investigator, other investigators, study staff, IRB members, IRB staff, the Research Subject Advocate, or any other Organizational officials.

- 3.2. Complaints may also be received through the IRB website, utilizing the “Report a Problem or Complaint” tab, or University of Nebraska’s ethics hotline EthicsPoint.
- 3.3. Any complaint that is received by the investigator or study staff that involves risk to participants or others, or changes the risk-benefit profile of the study, or which cannot be resolved by the investigator must be promptly reported to the ORA.
- 3.4. Any complaint that is received by the investigator or study staff that does not involve risk to participants or others, or does not change the risk-potential benefit profile of the study, and that is resolved by the investigator should be submitted in a summary format to the IRB at continuing review.

4.0 ORA Responsibilities

- 4.1. Complaints received by the ORA, or reported to the ORA by the investigators will be reviewed by the IRB Executive Chair and/or IRB Analyst. Complaints found not to relate to human subject research will be referred to the appropriate office (for example, to Nebraska Medicine or CHMC Patient Relations, or to UNMC or UNO Compliance Office).
- 4.2. Complaints related to human subject research will be further reviewed by the appropriate IRB Analyst. Additional information will be obtained from the complainant, the study documents, the investigator or research staff, or from other sources as appropriate. Based on this initial review, in consultation with the Executive Chair or designee, the IRB Analyst will determine:
  - 4.2.1. Whether the complaint represents an allegation of non-compliance, an adverse event, or an unanticipated problem involving risk. If so, the complaint will be handled in accordance with HRPP policy 8.1 (IRB Review of Adverse Events or Adverse Device Effects), HRPP Policy 8.3 (IRB Review of Unanticipated Problems Involving Risk to the Subject or Others), or HRPP Policy 8.4 (Review of Noncompliance Involving the PI and Study Personnel).
  - 4.2.2. Whether the complaint involves risk to participants or others, or changes the risk-benefit profile of the study. If so, the complaint will be reported and reviewed by the full IRB at a convened meeting {HRPP policy 2.2 (Full IRB Review)}.
  - 4.2.3. Whether additional actions need to be taken immediately to protect the rights and welfare of human subjects, in accordance with HRPP policy 8.6 (Study Hold, Suspension, and Termination).
- 4.3. The IO will be notified of all complaints which involve risk to participants or others, or which change the risk-benefit profile of the study.
- 4.4. The PI and other involved individuals will be promptly notified of the concerns expressed in the complaint, unless such notification would compromise handling of the complaint.

5.0 IRB Responsibilities

- 5.1. Complaints that do not involve risk to participants or others, or do not change the risk-benefit profile of the study are reported to the IRB (either at the time of continuing review, or as a special notification item).

- 5.2. Complaints that involve risk to participants or others, or change the risk-benefit profile of the study, or which cannot be resolved by the investigator will be reviewed by the full IRB at a convened meeting. The IRB will determine:
  - 5.2.1. Whether the complaint constitutes noncompliance per HRPP policy 8.4 (Review of Noncompliance Involving the PI and Study Personnel).
  - 5.2.2. Whether the complaint constitutes an unanticipated problem involving risk per HRPP policy 8.3 (IRB Review of Unanticipated Problems Involving Risk to the Subject or Others).
  - 5.2.3. Whether the research continues to satisfy the criteria for approval under 45 CFR 46.111, 21 CFR 56.111, and HRPP policy 2.5 (Criteria for IRB Approval).
  - 5.2.4. Whether further actions are necessary to protect the rights and welfare of human subjects. Such actions may include (but are not limited to):
    - 5.2.4.1. Requiring modification of the research protocol or the consent form
    - 5.2.4.2. Notification of current participants if such information may relate to participants' willingness to continue to take part in the research, with or without requiring re-consent.
    - 5.2.4.3. Requiring additional information be provided to past participants.
    - 5.2.4.4. Modification of the continuing review schedule.
    - 5.2.4.5. Monitoring of the research or the consent process.
    - 5.2.4.6. Study hold, suspension or termination.
    - 5.2.4.7. Referral to other organizational entities.

6.0 Reporting Complaints to Organizational 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).

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? Revised: 1/18/2023 - Clarified definition of "complaints"; noted additional policies related to complaints by research personnel or other interested parties regarding the functioning of one or more components of the HRPP; clarified that the ORA only investigates complaints related to human subjects research; added that complaints that do not involve risk to participants or others, or do not change the risk-benefit profile of the study are reported to the IRB (either at the time of continuing review, or as a special notification item); added comment that all required reports will be submitted to Institutional Officials and Federal Agencies in accordance with HRPP policy 8.7; reorganized sections; stylistic changes.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Revised: 5/8/2023 - Changed “IRB Administrator” to “IRB Analyst”{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

8.3 Review of Unanticipated Problems Involving Risk to the Subject or Others

1.0 Purpose

The purpose of this policy is to describe the process for reporting potential unanticipated problems (UPs) involving risk to the ORA and the IRB, and the process for review of potential UPs.

2.0 Policy

It is the policy of the organization that:

- 2.1. The ORA and the IRB will comply with HHS regulations at 45 CFR 46.108(a)(4)(i); any additional requirements of Common Rule agencies (as applicable); and FDA regulations at 21 CFR 56.108(b)(1), 21 CFR 312.32(a), and 21 CFR 812.3(s) (as applicable).
- 2.2. Any AE, UADE, noncompliance event, complaint, or other incident, regardless of the level of associated or potential risk, which appears to meet the criteria for classification as a UP will be submitted to the full IRB for review.
- 2.3. The convened IRB is responsible for determining whether the event, incident, outcome, or complaint meets the criteria for classification as a UP.

3.0 Definitions

- 3.1. Unanticipated Problems Involving Risk to Subjects or Others (UP) is defined as an event that meets the criteria below:
  - 3.1.1. The event is unexpected in terms of specificity, severity, or frequency, considering the nature of the research, the characteristics of the subject population, and the information contained in the protocol, protocol-related documents, and the ICF. In addition, the event is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject.
  - 3.1.2. The event is related, or possibly related to subjects' participation in the research or procedures involved in the research. This means there is a reasonable possibility that the event may have been caused by procedures involved in the research or resulted from participation in the research by the subject.
  - 3.1.3. The subject or others suffered harm, or were placed at greater risk of harm (including physical, psychological, economic, social, or legal) than was previously

known or recognized when the IRB approved the research either initially, at continuing review, or at the time of approval of a Request for Change.
    - 3.1.4. Though not a required criterion for definition of an event as a UP, the event generally warrants substantive changes 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.

Note: A UP may arise from an AE, UADE, noncompliance, complaint, or other incident (including new information such as IND safety reports, DSMB reports, or other outcome information).
Note: UPs may occur in research other than clinical trials, and may involve risks other than physical harm (for example, a stolen laptop or thumb drive containing identifiable information leading to risk of loss of confidentiality).

4.0 Investigator (or Other Reporters') Responsibilities

- 4.1. Reports of AEs/UADEs are submitted in accordance with HRPP policy 8.1 (IRB Review of Adverse Events and Adverse Device Effects).
- 4.2. Reports of complaints are submitted in accordance with HRPP policy 8.2 (IRB Review of Study Related Complaints).
- 4.3. Reports of noncompliance are submitted in accordance with HRPP policy 8.4 (Review of Noncompliance Involving the PI and Study Personnel).
- 4.4. IND safety reports, DSMB reports, or other outcome information on risk are submitted in accordance with HRPP policy 3.2 (Data and Safety Monitoring).
- 4.5. Reports of other unanticipated events related to the research that either expose subjects or others to potential risk or result in harm, but do not fall under the reporting requirements above must be promptly reported to the IRB as an Incident Report thru RSS.

5.0 IRB/ORA Responsibilities

- 5.1. The ORA will review reports under Section 4.1 thru 4.5 above in accordance with the criteria specified in HRPP policies 2.2 (Full IRB Review), HRPP policies 8.1 (IRB Review of Adverse Events and Adverse Device Effects), HRPP policies 8.2 (IRB Review of Study Related Complaints), and HRPP policies 8.4 (Review of Noncompliance Involving the PI and Study Personnel), and will make determinations (including referral to the convened IRB) as described in those policies.
- 5.2. Events reviewed by the ORA in accordance with the above policies will be referred to the convened IRB if a determination is made by the ORA that the event may constitute a UP.
- 5.3. The convened IRB will determine whether or not the event is a UP in accordance with Section 3.1 of this policy.
- 5.4. The IRB will ensure all necessary steps will be taken in order to protect the rights and welfare of human subjects and maintain compliance with applicable federal regulations and HRPP policies.

- 5.5. In addition to the required actions specified in HRPP policy 2.2 (Full IRB Review), IRB actions may include, but are not limited to:
  - 5.5.1. Requiring modification of the protocol.
  - 5.5.2. Requiring modification of the information disclosed during the consent process.
  - 5.5.3. Requiring notification of current participants when such information might relate to participants' willingness to continue to take part in the research.
  - 5.5.4. Requiring provision of additional information to past participants.
  - 5.5.5. Requiring current participants to re-consent to participation.
  - 5.5.6. Modification of the continuing review schedule.
  - 5.5.7. Monitoring of the research.
  - 5.5.8. Monitoring of the consent process.
  - 5.5.9. Referral to other organizational entities.

6.0 Reporting UPs 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).

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? Written: 4/4/2016 (Approved: 4/4/2016) - original author not recorded

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? Revised: 1/18/2023 - Clarified that certain events are always referred to convened IRB for review and determination if the event constitutes a UP, and other events are first reviewed by the ORA and only referred if determined by the ORA to be potentially represent a UP; simplified text; stylistic changes.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Revised: 5/8/2023 - Corrected regulatory reference in section 2.1; modified section 5.1 to reflect IRB actions as opposed to investigator actions (eg, "requiring modification of the protocol" as opposed to "modifying protocol"); correcting misspellings.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

8.4 Review of Noncompliance Involving the PI or Study Personnel

1.0 Purpose

The purpose of this policy is to describe the process for reviewing and reporting incidents of noncompliance by the PI, study team, and/or subjects. Noncompliance by the IRB and/or Other Components of the HRPP is addressed in HRPP 8.5 (Noncompliance by the IRB or Other Components of the HRPP).

2.0 Policy

It is the policy of the Organization that:

- 2.1. Reports of noncompliance with Federal Regulations, HRPP policies, or the requirements or determinations of the IRB, or the provisions of the IRB approved research study must be promptly reported to the ORA.
- 2.2. The PI is ultimately responsible for the proper conduct of research and for assuring that noncompliance is promptly reported in accordance with this policy, and for implementing any required corrective action plan.
- 2.3. Incidents of noncompliance will be promptly addressed by the ORA/IRB and appropriate action taken in order to ensure protection of the rights and welfare of research subjects.
- 2.4. Findings of serious or continuing noncompliance and suspensions or terminations of IRB approval as a result of noncompliance will be promptly reported to OHRP, FDA and sponsors or funding agency heads in accordance with the requirements of 45 CFR 46.108(a)(4), and 21 CFR 56.108(b), and the Organization's FederalWide assurance, as specified in HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

3.0 Definitions

- 3.1. Noncompliance is defined as any failure to follow federal regulations (including but not limited to 45 CFR 46, including any applicable subparts, or 21 CFR 50, 56), HRPP policies, the requirements or determinations of the IRB or the provisions of the IRB approved research study. Noncompliance may be serious and/or continuing, or neither

serious nor continuing. Noncompliance may be due to actions or inactions of the PI, study team, or subjects of the research. Noncompliance may also be classified as an unanticipated problem involving risk to the subject or others (UP) as defined in HRPP policy 8.3 (IRB Review of Unanticipated Problems Involving Risk to the Subject or Others).

- 3.1.1. Serious noncompliance is defined as a violation of applicable federal regulations, HRPP policies, or the determinations of the IRB which (a) significantly increases the risk to subjects, or otherwise compromises the rights and welfare of research subjects (including events that result in harm to a subject); or (b) appreciably decreases the potential direct benefit to subjects; or (c) compromises the scientific integrity of the research.
  - 3.1.1.1. In accordance with OHRP guidance, non-exempt human subject research conducted without IRB review and approval or without appropriate informed consent, or significant modifications to IRB-approved research without IRB approval is considered serious noncompliance.
  - 3.1.1.2. The IRB may decide that certain classes or types of noncompliance (for example, protocol violations involving drug dosing errors) represent serious noncompliance.
- 3.1.2. Continuing noncompliance is defined as (1) repeated incidents of the same or substantially similar noncompliance after the investigator or staff has been notified that the action represents noncompliance or despite appropriate retraining and/or a specific corrective action plan; or (2) repeated incidents of the same or substantially similar noncompliance of such a nature that the investigator should have reasonably been expected to know that such an action was noncompliance.

4.0 Reporting Noncompliance to the ORA

- 4.1. A report of noncompliance may be made by the PI or any member of the research team when they have direct knowledge that noncompliance occurred (eg, the research team reporting a violation of a research protocol by the research team, the subject or another). In these cases, there is no dispute about whether the event occurred, and the research team is reporting the noncompliance to the ORA.
  - 4.1.1. Reports of noncompliance should be made by submitting an Incident Report thru RSS
  - 4.1.2. Reports of noncompliance made by the PI or study team must be made to the ORA within ten (10) business days of the study team becoming aware of the event, or five (5) business days when the possible noncompliance was associated with harm to subjects or others.
- 4.2. A report of possible noncompliance may be made by any person (including a member of the research team) when there is an allegation that noncompliance occurred (eg, a person has reason to believe that the research team is not adhering to the protocol). Possible noncompliance may be later determined to have or not have a basis in fact.
  - 4.2.1. Reports of possible noncompliance should be made as soon as feasible.
  - 4.2.2. Persons reporting possible noncompliance may do so anonymously and may use any mechanism they wish to report to the ORA. This includes use of the “Report a Problem or Complaint” tab on the IRB website, or through other electronic reporting systems sponsored by the Organization.

5.0 ORA Responsibilities

- 5.1. Upon receipt of a report of noncompliance or possible noncompliance the following will occur:
  - 5.1.1. The ORA will conduct the initial investigation. Additional information will be obtained from the reporter, ORA or HRPP records, and/or from other sources as appropriate.
  - 5.1.2. If the initial investigation discloses that no noncompliance occurred, the IRB Analyst responsible will notify the reporter, and no further action need be taken.
  - 5.1.3. If the initial investigation confirms that noncompliance occurred, the IRB Analyst responsible, in consultation with the Executive Chair or designee, will determine:
    - 5.1.3.1. Whether the noncompliance may represent serious or continuing noncompliance
    - 5.1.3.2. Whether additional actions need to be taken immediately to protect the rights and welfare of human subjects, in accordance with HRPP policy 8.6 (Study Hold, Suspension, and Termination).
    - 5.1.3.3. Whether additional investigation is necessary, by the ORA, or by other parties including but not limited to the Institutional Compliance Officer (UNMC, UNO CHMC or BMC as appropriate), General Counsel, other IRB Analysts, other IRB members and internal consultants.
  - 5.1.4. If the report of possible noncompliance comes from someone other than the investigator the ORA will notify the PI (and other involved individuals) of the investigation, and the investigator will be provided an opportunity to provide any relevant information and/or records that should be considered.
  - 5.1.5. During the investigation, the investigator (or other relevant party) will have a reasonable opportunity to provide additional information.
  - 5.1.6. As appropriate, based on the nature of the noncompliance or possible noncompliance, the IRB, Institutional Official (IO) and Institutional Compliance Officer will be informed of any ongoing investigations as soon as is appropriate to do so.
- 5.2. After completion of the investigation by the ORA and review by the Executive Chair or designee, the following will occur:
  - 5.2.1. A report determined to be possibly serious or continuing noncompliance, will be referred to the convened IRB, along with the results of the investigation.
  - 5.2.2. A report determined to be neither serious, nor continuing will be sent to the convened IRB as a notification item.
- 5.3. Lists of protocol violations noted by a sponsor, CRO or Audit committee after a review of CRFs and other materials may be submitted to the ORA at the time of discovery, and will be reviewed by the ORA in consultation with the Executive Chair or designee. Incidents determined to be possibly serious or continuing noncompliance, will be referred to the convened IRB for action, and incidents determined to be neither serious nor continuing will be sent to the convened IRB as a notification item, as described above.

6.0 IRB Responsibilities

- 6.1. Noncompliance which may represent serious or continuing noncompliance will be referred for review by the convened IRB. The convened IRB will determine:
  - 6.1.1. Whether the incident represents serious and/or continuing noncompliance.
  - 6.1.2. Whether the incident is an unanticipated problem involving risk.
  - 6.1.3. Whether the corrective action plan is adequate.
  - 6.1.4. Whether the research continues to satisfy the approval criteria at 45 CFR 46.111 or 21 CFR 56.111.
  - 6.1.5. Whether subject accrual should be allowed to continue.
  - 6.1.6. Whether currently enrolled subjects should be notified of information related to the incident.
  - 6.1.7. Whether previously enrolled subjects who have completed participation in the study should be notified of information related to the incident.
- 6.2. After making the determinations above, the IRB may take action including, but not limited to:
  - 6.2.1. Requiring modification of protocol or consent forms, require notification and/or re-consent of enrolled subjects, institute monitoring of the research and/or the consent process, require more frequent continuing review.
  - 6.2.2. Auditing the research, or any of the investigator's other active or completed studies.
  - 6.2.3. Requiring additional investigator or study staff education and training.
  - 6.2.4. Suspending or terminating the research.
  - 6.2.5. Making recommendations to the IO regarding restrictions on, or termination of, other protocols submitted by the investigator, or regarding other sanctions against the investigator or staff including withdrawal or modification of pending or published manuscripts and/or destruction of research data or biological materials.
- 6.3. After completion of the review by the convened IRB the investigator (or other relevant party) will be informed of the results of the review, and of any determinations and requirements by the IRB.

7.0 Reporting Noncompliance to Organizational 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: 1/20/2016 (Approved: 1/20/2016) - original author not recorded

? Revised: 1/19/2018 - revision not documented

? Revised: 1/18/2023 - Simplified purpose statement; corrected regulatory citations in section 2.4; added caveat that reporting will occur in accordance with the Organization's FWA; clarified definition of noncompliance; clarified criteria for serious noncompliance in section 3.1.1; specified additional conditions which might be considered serious noncompliance (sections 3.1.1.1 and 3.1.1.2); clarified definition of continuing noncompliance; simplified description of reporting to ORA

(section 4.0); revised to separate and delineate responsibilities of ORA and of IRB; minimized specific details of processes associated with ORA and/or IRB review (moved to SOP); stylistic changes for clarity.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Revised: 3/8/2023 – Deleted reference to “minor” non-compliance and substituted “neither serious nor continuing”; minor revisions in wording of definition of non-compliance, serious non-compliance, and continuing non-compliance; changes “alleged non-compliance” to “possible non-compliance”; simplified section on reporting non-compliance to ORA; deleted list of types of people who may report non-compliance and of possible ways to report non-compliance; simplified section on ORA responsibilities; clarified method of reporting non-compliance discovered at time of CRO or other audit; stylistic changes {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Revised: 3/6/2024 – revised Title, Purpose (section 1), and section 3.1 to clarify that this policy includes noncompliance by research subjects; revised section 5.1.6 to clarify that IRB, IO and Compliance Officer informed of ongoing investigation as appropriate, based on nature of noncompliance. {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

8.5 Noncompliance by the IRB or Other Components of the HRPP

1.0 Purpose

The purpose of this policy is to describe the process for reviewing and reporting incidents of noncompliance by the IRB and/or other components of the HRPP.

2.0 Policy

It is the policy of the Organization that:

- 2.1. Reports of noncompliance with Federal Regulations related to human subjects research or HRPP policies by the IRB or other components of the HRPP shall be reviewed, investigated and reported as outlined below
- 2.2. Findings of serious or continuing noncompliance will be reported to OHRP, FDA and sponsors or funding agency heads in accordance with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b), and the Organization's Federalwide assurance, as specified in HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

3.0 Definitions

- 3.1. Noncompliance by the IRB or other components of the HRPP is defined as failure to follow federal regulations (including but not limited to 45 CFR 46, and applicable subparts, or 21 CFR 50, 56), HRPP policies, and/or Organizational policies. Noncompliance may be serious and/or continuing, or neither serious nor continuing.
  - 3.1.1. Serious noncompliance by the IRB or other components of the HRPP is defined as a violation of federal regulations, HRPP policies, and/or Organizational policies which (a) significantly increases the risk to subjects, or otherwise compromises the rights and welfare of research subjects, or (b) places the Organization at risk of significant regulatory, financial or reputational harm.
  - 3.1.2. Continuing noncompliance by the IRB or other components of the HRPP is defined as (1) repeated incidents of the same or substantially similar noncompliance, after the IRB or other component has been notified that the action represents non-compliance, or despite appropriate retraining and/or specific corrective action, or (2) repeated incidents of the same or substantially similar noncompliance of such a

nature that the IRB or other component of the HRPP should have reasonably been expected to know that such an action was noncompliance.

4.0 Responsibilities of the ORA, Chief Compliance Officer (CCO) and Institutional Official (IO)

- 4.1. Upon receipt of a report of noncompliance attributable to any component of the HRPP:
  - 4.1.1. The ORA will conduct the initial investigation. Additional information will be obtained from the reporter, ORA or HRPP records, and/or from other sources as appropriate.
  - 4.1.2. If the initial investigation does not confirm that noncompliance occurred, the ORA will prepare a report to the CCO describing the allegation, and explaining why it does not represent noncompliance. The CCO may accept the report and notify the IO and IRB, or may request clarification or additional information, or may conduct further investigation.
  - 4.1.3. If the initial investigation confirms that noncompliance occurred, the Executive Chair of the IRB, the Assistant Vice Chancellor for Regulatory Affairs or designee will prepare a report to the CCO describing the noncompliance. The report will classify the noncompliance as minor, serious and/or continuing and include a proposed corrective action plan (CAP) as appropriate.
  - 4.1.4. The CCO may:
    • Accept the report and CAP as proposed
    • Request modifications to the CAP
    • Request clarification or additional information
    • Conduct further investigation
  - 4.1.5 Upon conclusion of the investigation of noncompliance, a report of the noncompliance and the CAP will be presented to the IRB, IO and other organizational officials as appropriate.
- 4.2. The IRB Executive Chair/designee and/or CCO, as appropriate, will initiate all necessary action(s) to ensure that human subjects are fully protected, and the interests of the Organization are appropriately considered.
- 4.3. A record of the report and actions taken under this policy will be maintained by the ORA.

5.0 Reporting Noncompliance to Organizational 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).

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? Revised: 3/7/2023 – revised definitions; clarified that the ORA will conduct initial evaluation and pass recommendations to CCO; simplified throughout; stylistic changes.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Revised: 5/9/2023 – Deleted reference to “minor” non-compliance and substituted “neither serious nor continuing”; revised definition of serious non-compliance to include putting Organization at risk of significant regulatory, financial or reputational harm; revised definitions of serious non-compliance and continuing non-compliance to delete parts of the definition more appropriate for PI or research staff non-compliance; clarified possible actions of CCO.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

8.6 Study Hold, Suspension, and Termination

1.0 Purpose

The purpose of this policy is to describe the process for study holds, study suspensions, and study termination.

2.0 Policy

It is the policy of the Organization that:

- 2.1. The ORA has the authority to accept a study hold imposed by the PI, sponsor, DSMB, FDA or other funding agency, and the IRB Executive Chair or the IRB has the authority to release that hold.
- 2.2. The IRB or the Executive Chair has the authority to suspend IRB approval of research, and the IRB has the authority to release that study suspension.
- 2.3. The IRB or the Organization has the authority to terminate IRB approval of research.
- 2.3. Suspensions or terminations of IRB approval as a result of noncompliance will be promptly reported to OHRP, FDA and sponsors or funding agency heads in accordance with the requirements of 45 CFR 46.108(a)(4), and 21 CFR 56.108(b), and the Organization's FederalWide assurance, as specified in HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

3.0 Definitions

- 3.1. Study Hold: A planned or unplanned temporary halt to subject accrual and/or research activities, that is imposed by the PI, sponsor, DSMB, or FDA or other funding agency. A study hold may be full (affecting accrual and all study activities), or partial (affecting only accrual, or only some study activities).
  Note: A study hold which is not imposed by the IRB does not constitute a suspension or termination of IRB-approval of research under 45 CFR 46.113; 21 CFR 56.113.
- 3.2. Suspension of IRB Approval: A directive of the IRB at a convened meeting, or a directive of the IRB Executive Chair or designee (in consultation with the IO as appropriate), that all or some research activities in one or more protocols must be temporarily suspended.

Note: interruptions in human research resulting solely from the expiration of the IRB approval period does not constitute suspension of IRB-approval of research under 45 CFR 46.113 or 21 CFR 56.113.

- 3.3. Termination of IRB Approval: A directive by the IRB at a convened meeting that all research activities must permanently cease in one or more protocols.
- 3.4. Organization Directed Termination of IRB Approval: A directive by the Institutional Official (IO) that an IRB approved study be terminated.

4.0 Study Holds by PI, Sponsor, DSMB, FDA or Other Funding Agency

- 4.1. The PI, sponsor, DSMB, FDA or other funding agency may place a study hold by contacting the ORA by email or letter. When the ORA acknowledges the study hold subject accrual and/or research activities will cease in accordance with the conditions of the study hold.
- 4.2. The IRB will take appropriate action(s) to protect the rights and welfare of currently enrolled subjects.
- 4.3. The PI will be responsible for notifying all study personnel that there is a study hold and subject accrual and/or research activities may be restricted.
- 4.4. The IRB will be notified at the next convened meeting that a study hold was placed on the protocol.
- 4.5. The PI, sponsor, DSMB, FDA or other funding agency may request a release of the study hold by contacting the ORA by email or letter.
  - 4.5.1. If the study hold was initiated for subject safety concerns only the convened IRB may release the hold.
  - 4.5.2. If the study hold was initiated for other non-safety concerns, the IRB Executive Chair/designee may release the study hold.

5.0 Suspension of IRB Approval

- 5.1. The convened IRB or the IRB Executive Chair or designee may suspend IRB approval of research if such action is warranted due to concerns regarding the safety, rights, or welfare of human research subjects, investigators, research staff, or others, or due to noncompliance concerns, or other similar circumstances.
  - 5.1.1. The IRB Executive chair may exercise his/her authority to suspend research when, in his/her judgement, such action is necessary the protect the safety, rights, or welfare of human research subjects, investigators, research staff, or others before the next convened IRB meeting.
- 5.2. The IRB will take appropriate action(s) to protect the rights and welfare of currently enrolled subjects.
- 5.3. The PI will be responsible for notifying all study personnel that the study has been suspended and that all, or some, research activities are suspended.
- 5.4. The PI must report to the IRB any adverse events or outcomes associated with the suspension.
- 5.5. The PI must notify research subjects currently on study of suspension of IRB approval of research activities. Subjects should be advised of any follow-up necessary for safety

reasons.
- 5.6. The IRB, or the Executive Chair, has the authority to permit subjects currently on study to continue if it is in their best medical interest to do so.
- 5.7. If the study was suspended by the Executive Chair, the IRB will be notified at the next convened meeting of the suspension.
- 5.8. The PI may file a written appeal of the suspension to the IRB. The IRB has the final authority to act on any appeals and the decision of the Board cannot be overturned.
- 5.9. The convened IRB has the sole authority to release a study suspension.

6.0 Termination of IRB Approval

- 6.1. The convened IRB may terminate IRB approval of research if such action is warranted due to concerns regarding the safety, rights, or welfare of human research subjects, investigators, research staff, or others, which cannot be otherwise resolved, or due to serious or continuing noncompliance with the applicable federal regulations and HRPP policies, or due to other similar circumstances.
- 6.2. The IRB will provide the PI with written justification for termination of IRB approval of the research.
- 6.3. The IRB will promptly notify the IO and other appropriate Organization officials of the termination of IRB approval of research.
- 6.4. The IRB will take appropriate action(s) to protect the rights and welfare of currently enrolled subjects.
- 6.5. The PI will be responsible for notifying all study personnel that the study has been terminated and that all research activities must cease.
- 6.6. The PI must report to the IRB any adverse events or outcomes associated with the termination.
- 6.7. The PI must notify research subjects currently on study of termination of the study. Subjects should be advised of any follow-up necessary for safety reasons.
- 6.8. The PI may file a written appeal of the suspension to the IRB within 30 days of the termination. The IRB shall give the PI an opportunity to appear before the Board. The PI will be afforded due process and may bring legal counsel who will be restricted to observation only. The IRB has the final authority to act on any appeals and the decision of the Board cannot be overturned.

7.0 Organization Directed Termination of IRB Approval

- 7.1. In consultation with appropriate Organization officials the IO may direct that one or more of an investigator’s approved studies be terminated.
- 7.2. The IO will provide the PI with written justification for termination of the research.
- 7.3. The IO will notify appropriate the IRB Executive Chair, and Organization officials of the termination of the research.
- 7.4. The IRB will take appropriate action(s) to protect the rights and welfare of currently enrolled subjects.
- 7.5. The PI will be responsible for notifying all study personnel that the study has been terminated and that all research activities must cease.

- 7.6. The PI must report to the IRB any adverse events or outcomes associated with the termination.
- 7.7. The PI must notify research subjects currently on study of termination of the study. Subjects should be advised of any follow-up necessary for safety reasons.
- 7.8. The PI may file a written appeal of the suspension to the IO within 30 days of the termination. The IO has full authority to act on the appeal and may at his/her discretion seek consultation with the IRB or any other persons. The PI will be afforded due process and may be offered the opportunity to meet with the IO. The investigator may bring legal counsel who will be restricted to observation only. The decision of the IO regarding any appeal is final.

8.0 Reporting Suspensions and Terminations to OHRP, Department and Agency Heads, and FDA

Suspensions and terminations are reported in accordance with HRPP policy 8.7 (Reporting Incidents to Institutional Officials and Federal Agencies).

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? Revised: 1/20/2023 - Simplified Purpose statement; revised section 2.0 to reflect specific authorities granted in the body of the policy; removed reference to appeals panel and substituted option to seek consultation with the IRB or any other persons (section 7.8); stylistic changes. {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

8.7 Reporting Incidents to Institutional Officials and Federal Agencies

1.0 Purpose

The purpose of this policy is to describe the Organization’s requirements to ensure prompt reporting of incidents to Institutional Officials, Federal Agencies (including OHRP and FDA) and other Common Rule Departments and Agencies, and to AAHRPP.

2.0 Policy

It is the policy of the Organization that:

- 2.1. Unanticipated problems involving risk to the subject or others (UPs), serious or continuing noncompliance, suspensions of IRB approval, and terminations of IRB approval will be promptly reported to the Institutional Official (IO).
- 2.2. Unanticipated problems involving risk to the subject or others (UPs), serious or continuing noncompliance, suspensions of IRB approval, and terminations of IRB approval related to research subject to 45 CFR 46 and/or FDA regulations be reported to OHRP, FDA, and other Common Rule Department or Agencies, in accordance with 45 CFR 46.108(a)(4) and 45 CFR 46.113, and 21 CFR 56.108(b) and 21 CFR 56.113 as applicable.
- 2.3. Unanticipated problems involving risk to the subject or others (UPs), serious or continuing noncompliance, suspensions of IRB approval, and terminations of IRB approval related to research not subject to 45 CFR 46 and/or FDA regulations, will be reported to OHRP and funding agencies at the discretion of the Institutional Official.
- 2.4. The Organization will report to AAHRPP as soon as possible (but generally within 48 hours) after the Organization becomes aware of: (1) any negative actions by a government oversight office related to human research protections; (2) any litigation, arbitration, or settlements initiated related to human research protections; and (3) any press coverage of a negative nature regarding the Organization’s HRPP.

3.0 Definitions

- 3.1. Unanticipated Problems Involving Risk to the Subject or Others: as per HRPP policy 8.3 (IRB Review of Unanticipated Problems Involving Risk to the Subject or Others).
- 3.2. Serious Noncompliance: as per HRPP policies 8.4 (Noncompliance Involving the PI and Study Personnel) and 8.5 (Noncompliance by the IRB or Other Components of the HRPP).
- 3.3. Continuing Noncompliance: as per HRPP policies 8.4 (Noncompliance Involving the PI and Study Personnel) and 8.5 (Noncompliance by the IRB or Other Components of the HRPP).
- 3.4. Suspension of IRB Approval of Research: as per HRPP policy 8.6 (Study Hold, Suspension, and Termination).
- 3.5. Termination of IRB approval of Research: as per HRPP policy 8.6 (Study Hold, Suspension, and Termination).

4.0 IRB/ORA Responsibilities

- 4.1. The IRB Executive Chair/designee will submit all required written reports to the IO promptly (as appropriate in consideration of the nature of the event but no longer than 30 days following determination that the event is a reportable incident). Follow-up reports will be provided as necessary in conjunction with ongoing investigations.

5.0 Institutional Responsibilities

- 5.1. For research subject to the 45 CFR 46, the IO will submit all required written reports to OHRP and Department or Agency heads as appropriate promptly (as appropriate in consideration of the nature of the event but no longer than 30 days following determination that the event is a reportable incident). Follow-up reports will be provided as necessary in conjunction with ongoing investigations.
- 5.2. For research subject to FDA regulations, the IO will submit written reports to FDA promptly (as appropriate in consideration of the nature of the event but no longer than 30 days following determination that the event is a reportable incident). Follow-up reports will be provided as necessary in conjunction with ongoing investigations.
- 5.3. For research neither subject to 45 CFR 46 nor subject to FDA regulations, written reports may be submitted to FDA and/or OHRP and Department or Agency heads, at the discretion of the IO. The decision to report will be made by the Institutional Official after due consideration of recommendations of the IRB and the IRB Executive Chair.
- 5.4. Copies of the report (including any additional materials submitted to FDA, OHRP or Department or Agency heads) will be made available to the PI after submission.
- 5.5. Reporting events which occur at institutions not under the jurisdiction of the UNMC IRB are the responsibility of the external institution.
- 5.6. Reporting of events which occur at other institutions when UNMC acts as the reviewing IRB for that institution will be reported either by UNMC or by the relying institution, as described in HRPP Policy 1.3 (UNMC IRB Serving as the Single IRB for Multisite Research) and per the terms of the reliance agreement.

6.0 Investigator Responsibilities

- 6.1. For Federally funded research, it is the responsibility of the PI to notify the federal department or agency sponsoring the research. Any expenditure of federal funds during research which is not in compliance with federal regulations is prohibited. Verification of this notification must be provided to the IRB.
- 6.2. For commercially sponsored research, it is the responsibility of the PI to notify the sponsor and the Contract Research Organization (as applicable) and provide verification of this notification to the IRB.

7.0 Contents of Reports

- 7.1. Reports to the IO, OHRP, FDA and Common Rule Department or Agencies must include the information described in OHRP document “Guidance on Reporting Incidents to OHRP (2011)”, or any succeeding guidance.
- 7.2. Reports to FDA must also include IND or IDE number, if applicable.

8.0. Reports to AAHRPP

- 8.1. The ORA will report to AAHRPP as soon as possible but generally within 48 hours after the organization or any researcher (if the researcher is notified rather than the organization) becomes aware of:
  - 8.1.1. Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.
  - 8.1.2. Any litigation, arbitration, or settlements initiated related to human research protections.
  - 8.1.3. Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the Organization’s HRPP.
- 8.2. Investigators and research teams are responsible for notifying the ORA if they become aware of any of the actions noted above.

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? Revised: 8/15/2022 - Clarified that IO may (but is not required to) report incidents or noncompliance or UPs not associated with Federally funded research to Federal agencies; clarified that decision by the IO to report is made after due consideration of recommendations of the IRB, and in consultation with IRB Executive Chair and Organizational officials; clarified that copies of the

report will be made available to the PI after submission to the agencies; referenced HRPP 1.3 for reporting of incidents where UNMC is the IRB of record for other relying sites; reorganized lists of responsibilities for clarity. {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

? Board notified: 1/16/2023

? Revised: 8/1/2023 – added sections 2.4 and 8.0 regarding notification to AAHRPP.{Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}