1. PURPOSE

The intent of this procedure is to define the various types of noncompliance related to human subject research and detail processes for reporting and review of noncompliance and allegations of noncompliance.

2. SCOPE

This SOP applies to all human subject research conducted by researchers on staff at or affiliated with Aurora Health Care, conducted at any AHC facility, or utilizing individually identifiable data of AHC patients, whether that research is reviewed by Aurora's Institutional Review Board (IRB) or ceded to another IRB for review.

3. DEFINITIONS

NOTE: Terms not defined herein shall have the meanings set forth in the Aurora IRB's Glossary.

Noncompliance: The failure (intentional or unintentional) of an Investigator, his/her designees, IRB members, RSPP staff members, or others involved in the conduct or review of research involving human subjects to adhere to:

a) federal, state or local human subject protection laws, regulations, or policies;
b) Aurora system policy Research Involving Humans or Their Identifiable Specimens;
c) Aurora Research Subject Protection Program (RSPP) standard operating procedures governing the review and conduct of human subject research;
d) IRB determination; and/or
e) IRB-approved protocols, excluding changes made to eliminate apparent immediate hazard to subjects (see RSPP SOP Changes to Previously Approved Human Subject Research).

Noncompliance may be related to studies reviewed by Aurora's IRB as well as studies ceded to an external IRB. Noncompliance does not include failure by the study subject to follow protocol or investigator/study team instructions.

Examples of Noncompliance include but are not limited to:

a) Failure to obtain IRB approval prior to any protocol change
b) Failure to follow protocol (e.g., out of window visits, dosing error, lab processing error, inclusion/exclusion criteria error, etc.) except for those caused by study subjects (e.g., subject refused follow-up appointment, subject failed to take prescribed drug despite instructions, etc.)
c) Failure to obtain or document informed consent or failure to use the IRB approved consent form or other material;
d) Failure to obtain IRB approval for human subject research;
e) Failure to follow Aurora system policies on human subject research or RSPP/Aurora IRB SOPs;
f) Failure to follow study-specific IRB directives;
g) Failure of the IRB or RSPP caregivers to follow applicable regulatory requirements (e.g., make required determinations);
h) Inappropriate use of expedited review by IRB Chair or others.
Allegation of Noncompliance: An assertion (made by a second party) of Noncompliance that must be proven or supported with evidence to either confirm or deny.

Continuing Noncompliance: Noncompliance (Serious or non-serious) that continues to occur despite previous identification of the problem and subsequent corrective and preventive action, and which the reviewer or reviewing body, as applicable, has determined that, if allowed to continue, is likely to adversely affect the rights, welfare and/or safety of research subjects or adversely affect the scientific integrity of the study/data.

Research Misconduct: Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Research Misconduct does not include honest error or differences of opinion. See Aurora system policy #268 - Research Misconduct for definitions of fabrication, falsification and plagiarism.

Self-reported Noncompliance: Noncompliance reported by the individual or group responsible for the activity under which the Noncompliance occurred.

Serious Noncompliance: Noncompliance that in the judgement of the reviewer or reviewing body, as applicable, has been determined to:
(a) result in hospitalization or an irreversible, long-term, life-threatening or fatal medical occurrence, or require medical or surgical intervention to prevent one of these outcomes;
(b) Significantly increase the potential risk of harm to study subjects should the noncompliance recur;
(c) Significantly compromise subject rights; or
(d) Significantly impact the integrity of the study/data.

Significantly: In a way that is important enough to be worthy of attention or have an effect.

4. POLICY

4.1 Investigators, study team members, IRB members, Research Subject Protection Program (RSPP) caregivers and other Aurora caregivers have an obligation to report Noncompliance upon discovery.

4.2 Principal investigators have primary responsibility for reporting Noncompliance and for taking appropriate preventive and corrective action.

4.3 Noncompliance not reported by the individual or group responsible for the activity under which the Noncompliance occurred should be reported as an Allegation of Noncompliance by any individual who becomes aware of the Noncompliance.

4.4 Any Noncompliance reports or Allegations of Noncompliance related to human subject research will be investigated and appropriate action taken to ensure the safety and welfare of human research subjects.
4.5 Investigators, study team members, IRB members, RSPP staff and other Aurora caregivers shall cooperate in information gathering and reviews related to Noncompliance or Allegations of Noncompliance.

4.6 Allegations of Research Misconduct will be investigated in accordance with Aurora system policy Research Misconduct.

5. PROCEDURE

5.1 Reporting and Review of Self-reported Noncompliance

a) **What to Report.** Report anything meeting the definition of Noncompliance. *Note that Noncompliance does not include failure by the study subject to follow protocol or investigator/study team instructions.*

b) **When to Report.** All events or occurrences meeting the definition of Noncompliance should be reported as soon as possible but in no case later than 10 working days from the date of discovery.

c) **How to Report.** Noncompliance by the IRB, IRB member or RSPP caregiver should be reported to the Research Compliance Officer (RCO). Noncompliance by investigators, study team members or other Aurora caregivers engaged in the research should be reported to the RSPP Office. Reports should be submitted utilizing the noncompliance reporting form housed on the RSPP website. The reporter shall ensure the PI is aware of any report of noncompliance prior to or at the time of noncompliance submission.

d) **Initial Review - Determination of Severity and Corrective Action.** The RCO/designee (for Noncompliance by the IRB, IRB member or RSPP caregiver) or the RSPP Director/designee (for Noncompliance by investigators, study team members or other Aurora caregivers engaged in the research) will review the report of Noncompliance as soon as possible but in no case latter than 5 working days of receipt. The reviewer will obtain clarifying information as necessary and will determine and document severity (i.e., Serious Noncompliance, Continuing Noncompliance or other Noncompliance) based upon the definitions in section 3 of this policy. The reviewer will also assess the adequacy of any corrective and preventive action already taken and may require additional action. Corrective and preventive action is specific to the Noncompliance identified and for Noncompliance that is not Serious or Continuing typically may include investigator and/or caregiver education and training, study document or process revision, etc.

If unable to determine severity, the reviewer will consult with or refer the matter to the Chief Compliance Officer (for Noncompliance by the IRB, IRB member or RSPP caregiver) or IRB Chair/Institutional Official for Human Subject Protection.
(for Noncompliance by investigators, study team members or other Aurora caregivers engaged in the research), as applicable, for a determination.

i) **Determinations of Not Serious or Not Continuing Noncompliance.** The individual performing the initial severity review will report the outcome of any review that is determined to not be Serious or not Continuing Noncompliance to the: (1) reporter; (2) principal investigator of any related study; and (3) other caregiver(s) named in or otherwise involved in the Noncompliance, as applicable. The report will include any additional corrective or preventive action deemed necessary by the reviewer.

ii) **Determinations of Serious or Continuing Noncompliance.** The individual performing the initial severity review will report the outcome of any review that is initially determined to be Serious or Continuing Noncompliance to the: (1) reporter; (2) principal investigator of any related study; (3) other caregiver(s) named in or otherwise involved in the Noncompliance, as applicable; (4) the Institutional Official for Human Subject Protection; (5) Aurora’s IRB (for Noncompliance by investigators, study team members or other Aurora caregivers engaged in the research that is not ceded to an external IRB); and (5) the Research Compliance Committee (for Noncompliance by the IRB, IRB member or RSPP caregiver). The report will include any additional corrective or preventive action proposed by the reviewer. The reviewer may take immediate action or work with appropriate individuals (e.g., IRB Chair, Institutional Official, Chief Compliance Officer) to require immediate action deemed necessary to mitigate potential harm to research subjects or prevent immediate recurrence of the Noncompliance. Immediate action may include but is not limited to suspension of the study or suspension of specific study activities.

e) **Final Review - Determinations of Serious or Continuing Noncompliance**

i) **IRB Review for Studies Overseen by an Aurora IRB (Noncompliance by investigators, study team members or other Aurora caregivers engaged in research).**

The convened IRB will review initial determinations of Serious or Continuing Noncompliance by investigators, study team members or other Aurora caregivers engaged in research and provide a final determination and corrective and preventive action plan. The review will occur at the next available convened IRB meeting.

*Primary Reviewer’s Role.* A Primary Reviewer will be selected to present
the Serious or Continuing Noncompliance event to the convened IRB. The Primary Reviewer will summarize the important aspects of the event and provide a recommendation on whether the event meets the definition of Serious or Continuing Noncompliance and whether proposed corrective and preventive action is appropriate or additional action is necessary.

**Materials Provided to IRB Members.** Prior to the meeting, all IRB members are provided at a minimum:

1. A copy of the reported event or written summary of the allegation/finding of noncompliance and proposed corrective and preventive action;
2. A summary of the reviewer’s initial noncompliance determination;
3. The most recent IRB Submission Form, if appropriate; and
4. The current consent document, if appropriate.

The Primary Reviewer is also provided the complete protocol and other relevant materials, when appropriate.

**Convened IRB’s Role.** At the IRB meeting, the convened IRB will discuss the event and make the final determination of whether the event meets the definition of Serious or Continuing Noncompliance. The convened IRB will also consider the proposed corrective and preventative action and may require additional action. Additional action the IRB may require includes but is not limited to:

1. Obtaining more information pending a final decision
2. Education and/or training
3. Notification of current subjects when such information may relate to subjects’ willingness to continue to take part in the research
4. Providing additional information to past subjects
5. Modification of the information disclosed during the consent process
6. Requiring current subjects to re-consent to participation
7. Modification of the protocol or study processes
8. Modification of the continuing review schedule
9. Monitoring of the research or informed consent process
10. Suspension of the research
11. Termination of the research

The IRB will communicate its findings and any additional required action to the individual who reported the Noncompliance, the study’s principal investigator or any caregiver(s) named in or otherwise involved in the Noncompliance, and the Institutional Official.

ii) **IRB Review for Studies Ceded to a Non-Aurora IRB** (Noncompliance by investigators, study team members or other Aurora caregivers engaged
Initial determinations of Serious or Continuing Noncompliance for reports that are related to a ceded study will not be reviewed by Aurora’s IRB. RSPP will verify that the study team has reported to the IRB of Record any Noncompliance that is categorized as Serious or Continuing during the initial determination performed by the RSPP Director/designee. If this has not occurred, RSPP will direct the PI and individual submitting the form to do so.

### iii) Research Compliance Committee Review (Noncompliance by the IRB, IRB member or RSPP caregiver).

The Research Compliance Committee will review initial determinations of Serious or Continuing Noncompliance by the IRB, an IRB member or an RSPP caregiver and provide a final determination and corrective and preventive action plan. The review may occur via phone or email and will occur within three weeks of the initial reviewer’s determination whenever possible. The RCO will present the Noncompliance issue to the Committee, and the Committee will discuss the event and make the final determination of whether the event meets the definition of Serious or Continuing Noncompliance. The Committee will also consider proposed corrective and preventative action and may require additional action. Additional action the Committee may require includes but is not limited to:

1. Obtaining more information pending a final decision
2. Education and/or training
3. Re-review of items not reviewed in accordance with regulation or policy
4. Ceding review of items not reviewed in accordance with regulatory or policy to an external IRB
5. Notification of subjects when such information may relate to subjects' willingness to continue to take part in the research
6. Referral to the appropriate leader and/or Human Resources

The Research Compliance Committee will communicate its findings and any additional required action to the individual who reported the Noncompliance as well as the Institutional Official for Human Subject Protection, IRB, IRB Chair(s) and/or RSPP caregivers and their leaders, as applicable.
5.2 Reporting and Review of Allegations

a) **When to Report.** Allegation of Noncompliance may be reported at any time. However, if an Allegation is received for a Noncompliance that is self-reported within a reasonable timeframe (even if past the due date), the originator of the Allegation will be notified and the Allegation will be dismissed.

b) **How to Report.** Allegations of Noncompliance should be reported to the RCO. Reports should be submitted via email, or for those wishing to remain anonymous, via the Compliance Hotline.

c) **Review of Allegations**

i) **Determining Whether Alleged Noncompliance has a Basis in Fact.** Allegations of Noncompliance will initially be reviewed by the RCO as soon as possible but in no case later than 5 working days of receipt. The RCO will convene a panel of reviewers consisting of the Institutional Official for Human Subject Protection/designee, RSPP Director/designee, and ARI Director/designee. The RCO may adjust the membership of the panel to address potential conflicts of interest, needed expertise, etc. Investigations into whether the Allegation has a basis in fact and meet the definition of Noncompliance will be completed within 30 days from receipt of the Allegation unless an extension is agreed to by the Chief Compliance Officer for purposes of additional fact gathering. The RCO/designee may gather or assign a panel member/designee responsibility for gathering information for the panel. The RCO/designee will notify the investigator or any caregiver(s) named in or otherwise involved in the Allegation before conducting the investigation. The panel of reviewers will respect the confidentiality of the individual reporting the Allegation as well as those named in or otherwise involved in the Allegation. The panel may deliberate in person, via phone or email.

ii) **Determined to be Based in Fact.** If the panel of reviewers determines that the Allegation has a basis in fact and meets the definition of Noncompliance, the RCO/designee will document and communicate the determination to the individual who reported the Allegation as well as the principal investigator or any caregiver(s) named in or otherwise involved in the Allegation. The RCO will complete a Noncompliance report utilizing the mechanism and within the timeframes noted in sections 5.1.a) & b). The RCO will work with the principal investigator or any caregiver(s) named in or otherwise involved in the Noncompliance to propose a corrective and preventive action plan. Determination of severity of Noncompliance and corrective and preventive action will be conducted in accordance with sections 5.1.c) & d).
iii) **Determined not to be Based in Fact.** If the panel of reviewers determines that the Allegation does not have a basis in fact, the RCO/designee will document and communicate the determination to the individual who reported the Allegation as well as the principal investigator or any caregiver(s) named in or otherwise involved in the Allegation.

iv) **If Unable to Determine if Based in Fact.** If the panel is unable to determine whether an Allegation has a basis in fact and/or meets the definition of Noncompliance or is otherwise unable to adequately investigate an Allegation, the RCO/designee will consult with and/or defer the matter to the Chief Compliance Officer or the Institutional Official. After a determination is made, the RCO/designee will take the steps noted in 5.2.c)ii) or iii), as applicable.

### 5.3 Dispute Resolution.

If there is disagreement about the initial determination of Noncompliance, the corrective or preventive action required, or if there is any other disagreement about the Noncompliance investigation or determination, the matter will be referred to the following individuals for resolution: (1) if the initial review was conducted by the RSPP Director/designee, the issue will be referred to the IRB Chair or Institutional Official for Human Subject Protection; (2) If the initial review was conducted by the Research Compliance Officer, the issue will be referred to the Chief Compliance Officer.

### 5.4 Additional Noncompliance Reviews

a) **IRB Summary Review of All Noncompliance.** On an at least annual basis RSPP will provide to the IRB a summary report of all Noncompliance.

b) **Annual Prioritization of Research Monitoring and Education.** On an annual basis, RSPP will provide a summary of the various types of Noncompliance (e.g., dosing errors, data sharing/protection issues, informed consent errors, etc.) to the Council for Quality Assurance and Improvement in Research (CQAIR). CQAIR may use this data to determine monitoring and/or education priorities.

### 5.5 Reporting to Regulatory Agencies and Institutional Officials

All findings of Serious or Continuing Noncompliance will be reported via written communication to regulatory agencies and institutional officials, and others as applicable, in accordance with the SOP 408.
NONCOMPLIANCE IN HUMAN SUBJECT RESEARCH

CROSS REFERENCES:
- RSPP SOP 408 – External Reporting
- RSPP SOP 409 – Reliance on External IRB

OWNER:
Director, Research Subject Protection Program

REFERENCES:
- 21 CFR 56.108(b)
- 45 CFR 46.103(b)(5)
- OHRP Guidance on Written IRB Procedures (July 1, 2011)
- AAHRPP Element I.5.D.