14.1 NON-COMPLIANCE

A. Definitions

Non-compliance is a violation of or failure to comply with federal regulations, state laws, or Institutional policies governing the protection of research subjects. This may include some deviations from the protocol as approved by the IRB, violation of IRB requirements or any conditions imposed by the IRB on the condition of approval.

Serious non-compliance is any action or omission in the conduct of research that adversely affects the rights and welfare of research subjects, significantly increases risks to participants, decreases potential benefits, or compromises the integrity or validity of the research data.

Continuing non-compliance is a pattern of non-compliance that persists after the investigator has knowledge of the problem or a failure to respond to a request from a regulatory authority to resolve an issue. Continuing noncompliance suggests lack of understanding or disregard of Institutional policies or applicable regulations that protect the rights and welfare of participants, the Institution, and others. This includes a possible systemic deficiency or a failure to correct previously identified non-compliance.

Allegation of Noncompliance is an assertion of noncompliance that has yet to be proved or supported by evidence.

B. Reporting Requirements

Non-compliance is a failure to comply with laws, regulations, Institutional policies, or the requirements or determinations of the IRB. All investigators and study staff are required to report incidences of non-compliance to the IRB. Non-compliance may include protocol deviations, research participant complaints, and/or audit findings. Minor protocol deviations that did not increase risk to subjects may be reported to the IRB at the time of Continuing Review. Suspected serious or continuing non-compliance must be reported as soon as possible, within 10 days of PI knowledge of the Incident, by submitting an Incident through the electronic IRB system. Such reports should describe the circumstances of the Incident, any corrective actions, as well as actions implemented to prevent the recurrence of similar incidents in the future.

Non-study staff should discuss any concerns regarding compliance with rules and regulations that govern the conduct of human subject's research with their manager and/or the responsible PI.

Reports of allegations of non-compliance may also be communicated directly to the IRB or ORIC through one of the following mechanisms:

i. Contacting the IRB Chair, the Director, ORIC, or an ORIC staff member via phone, e-mail, letter, or in-person.

ii. E-mailing IRB@luriechildrens.org.

iii. Calling the Institution's anonymous Compliance hotline (800) 273-8452 or the Corporate Compliance Office.

The identity of an individual reporting an allegation of noncompliance will be protected to the extent possible. This identity protection remains even if the concerns or allegations are found, upon investigation, to be without merit.

C. Investigations

i. Initial Review:

a. An initial review of all reports received is conducted by a member of the ORIC staff under the direction of the Director, ORIC and/or IRB Chair, or designee.

b. In some cases, it may be necessary to take interim measures to protect human subjects or to preserve federal or other sponsor funds. In such cases, the Director, ORIC, the Research Integrity Officer (RIO) , and the IRB Chair determine the appropriate interim measures.

ii. Determining Need for Investigation:

The Director, ORIC and IRB Chair, or designee, may determine the following after the initial review:

a. That the suspected non-compliance is neither serious nor continuing. ORIC staff and the IRB Chair, or designee, will confirm appropriate corrective and preventive actions have been implemented and will acknowledge the report and return documentation to the PI.

b. If the matter represents potentially serious or continuing non-compliance as defined above, the Director, ORIC, in consultation with the IRB Chair will determine the need for an investigation. Investigations may be initiated as a result of information received from a variety of sources. The Director, ORIC keeps the RIO informed, as appropriate, during this initial review and initiates preliminary discussion with involved parties. Documentation of all allegations of non-compliance, subsequent investigations, and resultant correspondence is maintained by ORIC.

iii. Investigation

Upon determination that an allegation of suspected noncompliance has a basis in fact, a formal investigation is required, the Director, ORIC will appoint the appropriate staff to conduct the investigation. The ORIC staff will have the necessary expertise to carry out a formal investigation and evaluation of the relevant evidence. The appointed staff will not have any personal, professional, or financial conflicts of interest. All investigations are handled in a confidential, sensitive, and timely manner.

ORIC staff will notify the PI of the determination of the required investigation in writing and will request the PI to provide additional information in order to gather additional facts (i.e. an audit of the study records). This may also include a request to interview the PI, the research study staff, and/or other members of the human research protection program (HRPP).

Upon receipt of notification, the PI must provide access to the requested study documents, such as the protocol versions, IRB application, consents, subject study files, source documents, logs, monitoring reports, relevant communication, etc.

iv. Review of Findings

Upon completion of the investigation, the Director, ORIC and IRB Chair or designee will evaluate all findings for confirmation of serious and/or continuing non-compliance.

v. Possible Actions and Outcomes

If the investigation results in a determination of serious or continuing non-compliance, the Director, ORIC will notify the RIO. The ORIC staff conducting the investigation may propose a corrective and preventive action (CAPA) plan. These will be reviewed by the Director, ORIC, the RIO, and IRB Chair or designee and adjusted as necessary. The proposed CAPA may include, but is not limited to, one or more of the following:

a. Require modifications to the protocols and/or consent documents, including notification to the enrolled subjects and the requirement to re-consent subjects;

b. Require implementation of specified corrective action measures;

c. Require attendance by the PI and/or other research personnel in tailored education sessions provided by ORIC or continuing education provided by vetted external entities (e.g. CITI modules, FDA provided training, etc.);

d. Require audits of other active research studies conducted by the PI, study staff, and/or department/division;

e. Increase routine monitoring by compliance staff;

f. Modification/shortening of the approval period;

g. Mandated oversight or mentoring by a senior investigator;

h. Monitor the informed consent process;

i. Determination that data collected may not be used for further study and/or publication;

j. Temporary halt of enrollment in the study pending implementation of corrective action;

k. Temporary suspension of all research activity pending implementation of corrective action;

l. Termination of IRB approval;

m. Limitation or revocation of the investigator/study staff's privilege to conduct human subjects research at the Institution; and/or

n. Other action deemed appropriate by the IRB.

D. IRB Reporting and Responsibilities

The IRB's main role and responsibility in events of non-compliance in human subjects research is to ensure the rights and welfare of research participants are protected. If the Director, ORIC and IRB Chair/designee determines that the event represents serious and/or continuing noncompliance, the IRB will be provided with relevant materials (i.e., background information, findings of the investigation, the draft CAPA action plan, etc.) to facilitate an informed discussion and decision at the convened IRB. The IRB will review the Incident and recommended CAPA to determine the root cause and adequately protect research participants. The IRB may vote to approve the CAPA as proposed or may require additional actions.

E. Principal Investigator Responsibilities

Principal investigators are responsible for reporting non-compliance on their protocols. They may choose to initiate, voluntarily, a suspension or termination of enrollment of study activities until all issues are investigated and resolved. Such a voluntary action does not constitute a suspension of IRB approval.

Investigators are informed when an allegation or complaint has been received on one of their protocols, and they are required to fully cooperate with any investigation or requests for information, and maintain all related records pending the outcome even if policies or regulations would otherwise allow the destruction of the records. The investigator is responsible for responding promptly and in writing to all questions and issues raised including a plan of action to prevent the incident from occurring in the future.

F. Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. The ORIC Director, or the IRB Chair will promptly notify the PI of any IRB decision to suspend or terminate a research study. The notification will include the reasons for the suspension or termination. For a suspension, the notification will include a description of any actions to be taken before the suspension may be lifted.

If the IRB decides to suspend or terminate its approval of a research project, the IRB will ascertain whether there are subjects enrolled in the research. If there are currently enrolled subjects, the IRB will work with the PI to ensure that a plan is in place to appropriately notify subjects and that procedures for subject withdrawal consider the rights and welfare of those subjects. IRB decisions for suspension or termination of approval will be reported to the IO.

G. Reporting Requirements

In the event that serious or continuing non-compliance is identified, the Director, ORIC will work with the RIO/IO to report the non-compliance to external regulatory agencies, in accordance with applicable federal, state, and local laws. Once a reportable event has been identified and the letter has been drafted, they will consult with the Corporate Compliance Office and/or the Office of General Counsel for review. The report is to be filed promptly (i.e., typically within 30 days of recognition of the reportable event). The final report and related documents are filed and maintained by the ORIC office.

External entities include, but are not limited to:

- Office for Human Research Protections (OHRP) - if the study is subject to U.S. Department of Health and Human Services (DHHS) regulations;
- Other federal agencies when the research is subject to those agencies and the agency requires reporting separate from that to OHRP (e.g. Department of Defense components, etc.);
- Food and Drug Administration (FDA) - when the research is FDA-regulated;
- Sponsors of the research - as appropriate; and/or
- Funding source of the research - as appropriate.

14.2 INSPECTIONS BY REGULATORY AGENCIES

Certain regulatory authorities, funding and accrediting agencies have the authority to inspect study records and the operations of the IRB. It is the expectation of the Institution that investigators and research staff, ORIC, and the IRB will cooperate with inspections conducted by external agencies in compliance with these regulations. The PI or designee should notify ORIC when an external audit is expected. ORIC will notify additional entities within the Institution as appropriate and will provide support preparing for and during the audit.

Reports of external inspections of research records are to be submitted to ORIC. The Director, ORIC, in consultation with the additional Institutional entities (e.g. IO, IRB Chair, General Counsel, Corporate Compliance, Privacy Officer, etc.) will assist the PI in addressing any findings and responding to the regulatory agency.

Copies of external inspection reports are to be maintained by the PI and/or ORIC according to the IRB Record Retention Policy.