Institutional Review Board Policies and Procedures Manual

SECTION 9: TYPES OF IRB SUBMISSIONS AND IRB REVIEW

9.1 TYPES OF IRB SUBMISSIONS

Before an investigator may initiate any research activity that involves human subjects, the investigator is required to obtain either approval from the IRB for the research activity or obtain a determination that the research is exempt from the requirement of IRB review and approval.

Definitions:

Human subject: A living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Research: A systematic investigation designed to contribute to generalizable knowledge.

A. Non-Human Subjects Research

The IRB may determine that an activity does not meet the criteria for research involving human subjects as defined in the federal regulations at 45 CFR 46.102. "Projects that do not involve "human subjects" and/or are not considered "research," as described above, do not require review by the IRB. Submissions determined not to meet both criteria will be issued a "Not Human Subjects Research" determination and letter.

Research involving coded or de-identified private information or specimens is considered non-human subjects research when the private information or specimens cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(e) if the following conditions are both met:

i. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

ii. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

   a. the investigators and the holder of the key entered into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);

   b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

   c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

*Note that information associated with a specimen that is coded according to the standards above (per OHRP guidance) may not necessarily meet the definition of de-identified under the HIPAA Privacy Rule. For example, if the code is derived from a patient identifier or certain data elements, such as dates of service or zip codes, the use or disclosure of the information

for research may still require HIPAA authorization or waiver of authorization, or, if the information constitutes a "limited data set," a data use agreement with the recipient of the information. Non-human subjects research does not require an exempt determination by the IRB as it does not constitute research involving human subjects as defined in CFR 46.102(e)).

Investigators who have questions related to this policy, such as what is considered identifiable information or are unsure of whether their research involves human subjects, should contact ORIC for guidance.

Note: this policy does not apply to human embryonic stem cells.

B. Case Reports

Case reports may or may not be considered research. A starting point is to consider whether the case report contains the elements of research (i.e., it specifically involves a *systematic investigation* with the intent to contribute to *generalizable knowledge*).

Simply summarizing an interesting treatment, presentation, or outcome of a patient, does not constitute research. Typically, when a case report is presented to share information for medical educational purposes or to request advice from colleagues on the clinical care of a patient or group of patients during a departmental meeting, conference, or other accepted venue for discussion of clinical management, it would not be considered a research activity and does not require IRB approval. However, when the intent is to evaluate a specific hypothesis (e.g., a hypothesis is generated in advance of a retrospective records review), this activity constitutes research.

ORIC staff is available to assist with the determination if a case report/case series meets the definition of human subjects research and requires IRB review. If requested, ORIC staff may provide a letter documenting the determination that the case report/case series did not meet the definition of human subjects research and does not require IRB review. To obtain this letter from ORIC, a completed Initial application in the electronic IRB system for the Case Report/Case Series .

It should also be noted that case reports must always be prepared in accordance with the requirements of the HIPAA privacy rule. Any access to or disclosure of Protected Health Information (PHI) in the case report must be done with the patient's authorization or, if the patient is deceased, authorization of the patient's family. If no PHI is disclosed, this does not apply.

C. Human Embryonic Stem Cells

Due to the ethical and moral implications surrounding the field of embryonic stem cell research, ORIC and the IRB have adopted this policy for proposals involving this area of research. The NIH defines "human embryonic stem cells (hESCs) as "pluripotent cells that are derived from early stage human embryos, up to and including the blastocyst stage, are capable of dividing without differentiating for a prolonged period in culture and are known to develop into cells and tissues of the three primary germ layers." Prior to beginning any work with hESCs, PIs are required to submit their proposals to the IRB for review. The IRB Chair, in collaboration with the Director of ORIC, will determine whether the project is considered exempt, or if expedited or full board review is warranted. An Investigator cannot make this

determination. When submitting a proposal involving the use of embryonic stem cells, the following items are required:

i. Initial Application in electronic IRB system:

a. Justification for exempt status based on the exempt status categories as defined in 45 CFR 46.104.

b. Identification of the clinic that will supply the embryos and obtain a copy of all clinical informed consent documents. If the clinic is affiliated with an academic institution, the IRB approval documents and Federalwide Assurance (FWA) number is to be provided.

c. Description of how the embryos will be obtained, and whether they are considered donated or discarded. The clinical informed consent document must contain information regarding donation of embryos to research. In Vitro Fertilization (IVF) clinic consent forms are to inform the donors regarding any use of their donated or discarded embryos for research purposes.

d. Documentation that the clinician at the IVF clinic has agreed to donate the embryos for use in the research project(s).

e. ESCRO Committee Review: In addition to the above requirements, the PI must submit the proposal to the Northwestern University Embryonic Stem Cell Research Oversight (ESCRO) committee for their review.

D. Human Subject Research

The IRB must review and approve all research involving human subjects.

The three levels of review include exempt, expedited, and full board review. For each submission ORIC requires the appropriate application completed in the electronic IRB system.

i. Application for IRB Exemption

Under the federal regulations, certain types of research are exempt from IRB review. Exemption from IRB review does not imply that an investigator is free from the ethical responsibility to human subjects who are part of the research; it signifies only that IRB review and (continuing) approval of the research is not required by federal regulations. The investigator is not permitted to make an exempt determination for their human subjects' research; instead, the investigator is required to submit a study using an Initial application in the ,electronic IRB system. This application outlines the criteria used for determining whether a study qualifies for an exempt determination. If the reviewer determines that a study meets the criteria, a letter is sent to the PI informing them of the determination and responsibilities.

ii. Initial Submissions for Expedited or Full Board Review

All Institutional investigators proposing to initiate a research activity involving human subjects must submit an Initial application in the electronic IRB system. The ORIC and IRB review under expedited and full board is a comprehensive evaluation of a research project that determines whether it is ethical to involve human beings as subjects based on the criteria for approval listed in federal regulations 45 CFR 46.111 and 21 CFR 56.111.

Research investigators and department heads will consider whether the research will involve human subjects as defined in 45 CFR 46.102. The research investigators may then submit to ORIC any research protocols that involve human subjects for a determination.

The Initial application submission in the electronic IRB system should contain all required protocol documents, including the following in the electronic IRB system:

a. Protocol: If the research activity is occurring at multiple sites, a multi-center protocol may exist. A full study protocol is to be uploaded if the convened IRB needs to review the application.

b. The Investigational brochure (IB) and/or previous data on the investigational agent for study under a new drug application (IND) 21 CFR 312.23(a)(5) and 312.55). For investigational devices, technical information, such as product inserts, manuals, and instructions for use, and other relevant material to evaluate the risk determination of the device. In addition, the IND/IDE letter issued from the FDA is also to be uploaded into this application.

c. Parental permission, adult consent, and adolescent assent forms: See the section 11 of the Policy and Procedure manual for more information about obtaining informed consent.

d. Research Safety Reviews:

- A letter from the Radiation Safety Committee (RSC) is required to be uploaded into the Initial application when the research involves administration of radiopharmaceuticals or radioactive materials when the radioactive drug is experimental or is administered for research purposes only. If the research uses ionizing radiation without direct clinical indication, this also requires RSC approval.
- A letter from the Institutional Biosafety Committee (IBC) is required to be uploaded into the Initial application if the research involves recombinant or synthetic nucleic acid molecules (r/sNA) molecules and biohazard agents.

e. Recruitment Material: any material that will be distributed to subjects or publicly posted containing information about the study is to be uploaded into the application. Documents will be reviewed and approved as part of the initial review. After a study is initially approved, new recruitment materials added will need to be submitted via a Modification application in the electronic IRB system.

f. Study Questionnaires, Surveys, and Diaries: any surveys, questionnaires, or diaries, which will be utilized in the research, are to be uploaded into the application.

iii. Renewal Submissions

Periodic review is required for ongoing research protocols at intervals appropriate to the degree of risk. The frequency and extent of periodic review for each study is based on the nature of the study, the degree of risk involved, the novelty of the research procedures, and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be reviewed by the IRB.

Some research does not require annual review, and the IRB reviewer will document this per study. The IRB reviewer may request annual review and will document the protocol specific reasoning for this requirement. Reasons may include but are not limited to:

- Study staff Conflicts of Interest
- Risk to study population
- Study design
- Non-compliance

Studies not required to submit annually to the IRB will be issued a 3-year approval period. During this time, the PI and study team must still:

- Ensure all personnel comply with their HSR/GCP education requirements
- Submit any modifications to the study to the IRB for review prior to implementation
- Promptly report any Unanticipated Problems/Adverse Events/Protocol Deviations to the IRB for review
- Submit a Closure when the study is complete

Upon expiration of the 3-year approval period, if the study is still open and active, a Renewal must be submitted to the IRB for review.

Each IRB approval notice designates a period of time during which activities involving human research subjects may be undertaken. No research project may continue to recruit, enroll, or treat subjects or analyze data after the expiration date of the IRB approved research unless the IRB finds an overriding safety concern or ethical issue such that it is in the best interest of the participants to keep participating. Continuation of the research after midnight on the date of expiration of IRB approval is a violation of federal regulations.

To assist an investigator in fulfilling the requirement for Renewal, the investigator receives at least one notice from ORIC notifying them of the upcoming expiration date.

The IRB performs periodic review in order to monitor previously approved research to document that the protocol continues to protect sufficiently subject safety and welfare. A second objective of periodic review is to confirm that all information presented to subjects is complete, accurate, and up-to-date.

To fulfill this function, IRB requires that each investigator complete a Renewal application in the electronic IRB system, which provides a summary report on the progress of the research to date, including, but not limited to, the following:

a. A summary that contains relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval;

b. The number of subjects enrolled at the Institution and at all sites (if applicable);

c. Description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research that were not previously reported;

d. Any recently published literature, new findings, or other relevant information; especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;

e. A copy of the current stamped informed consent documents; and

f. Any relevant multi-center trial reports (data safety or clinical research organization monitoring reports).

As in their initial review, the IRB must evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of subjects' privacy and data confidentiality, safety monitoring procedures, and additional protections for vulnerable populations in order to determine the research continues to meet the criteria for approval outlined in 45 CFR 46.111 and 21 CFR 56.111.

iv. Modification Submissions

Amendments to approved research studies must be submitted to the IRB via a Modification application in the electronic IRB system, with both annotated and clean versions of revised documents. The IRB approval will indicate if it is necessary for active participants to be re-consented with the revised informed consent form. Please see IRB Policies and Procedures Manual Section 11 for more information on the requirement of re-consent/assent.

Proposed changes may not be implemented until the IRB has reviewed and approved the Modification, except when the changes are necessary to eliminate immediate hazards to subjects. In this case, the Modification must be submitted to the IRB within 72 hours and include the reason immediate action was taken. These changes will be reviewed by the IRB to determine if this was appropriate and consistent with ensuring the continued welfare of participants.

Note: Information on significant new findings that present potential of an increase in risks to participants (i.e., revised investigational brochure, protocol, etc.) or identify new risks are to be provided to active research participants immediately and their willingness to continue to participate confirmed. This communication should be well documented. As above, once the IRB reviews and approves the Modification and consent forms, active participants should be formally re-consented.

v. Unanticipated Problems and Adverse Event Reporting

Investigators are required to submit reports of all serious and unexpected adverse events experienced by human subjects that meet the criteria for reporting. These are to be submitted via an Incident Report in the electronic IRB system. Please refer to the Section 13 Data Safety Monitoring and Regular Reporting Requirements.

vi. Other Submissions

Any information relevant to the participation of human subjects in a proposed or approved research project in which the Institution (including its employees or physicians) is engaged should be submitted for review and if appropriate for review by the IRB. Examples of relevant materials include, but are not limited to documentation of temporary study suspension by the sponsor or PI, clarification of subject complaints, audit reports, study

drug shortages, or notice of FDA approval of study drugs or devices. In some cases, these materials may require consideration by the convened IRB. In each instance, the IRB will determine whether the new information should be relayed to enrolled subjects.

vii. Study Inactivation

Investigators are required to close the study with the IRB once all study activities have been completed to terminate the IRB approval. Research studies may not be inactivated if any of the following are true:

a. Enrollment, research-related interventions, and/or participant follow-up at the Institution are ongoing;

b. Data analysis or manuscript preparation is ongoing and involves the use of, or access to, personally identifiable information or protected health information;

c. Biological specimens containing individually identifiable information are being maintained in a repository that has been approved as part of the study or upon which analysis or research is ongoing at the Institution (If specimens were transferred to a separate repository that has ongoing IRB approval, the study may be closed);

d. Permission from an external sponsor to close the study has not been received.

Investigators who wish to inactivate their studies with the IRB are to submit a Closure application via the electronic IRB system. Once the Closure has been approved by the IRB, study records must be kept for:

e. 3 years post inactivation per Institutional policy;

f. 2 years post drug/device approval or program closure per FDA policy (21 CFR 312.57);

g. As specified by the study contract or as stipulated by the study sponsor

For all studies where consent was not obtained and private health information was collected, study databases should be de-identified and any correlation tools that link the de-identified data to the identifying information should be destroyed.

9.2 TYPES OF IRB REVIEW

A. Administrative Pre-Review

Research Compliance Coordinators (RCCs) conduct administrative and regulatory reviews of all submissions (Initial applications, Renewals, and Modifications), prior to forwarding the submission to the IRB Chair/Vice Chair or IRB for consideration. The review evaluates the submission for completeness and compliance with federal regulations, Institutional and ORIC policies, including IRB policies and procedures to minimize situations where time and effort are spent considering submissions that do not meet the regulatory criteria for IRB approval. As part of this process, the RCC works with research staff to update and modify submissions with the goal of addressing all regulatory and Institutional requirements. As needed, additional consultation may be sought from the IRB Chair(s), designated members, or others having expertise with the issues identified.

The RCC will not forward incomplete submissions to the IRB for review. These are returned to the PI to address outstanding items. Exceptions to this policy are issued at the sole discretion of the Director, ORIC, and are made on a case-by-case basis and only in extraordinary circumstances. Administrative items and issues identified during the RCC review are communicated to the PI so that any outstanding items or issues identified by the RCC are addressed prior to IRB Chair/Vice Chair or full IRB review. At the time a submission is deemed complete, the assigned RCC forwards the submission for the appropriate level of review by the IRB at a convened meeting, IRB Chair, Vice-Chair(s), or the designated reviewer for cases where the research activity may be considered exempt.

Initial ORIC and IRB review is a comprehensive evaluation of a research project that determines whether it is ethical to involve human beings as subjects based on the criteria for approval listed at 45 CFR 46.111 and 21 CFR 56.111. If responses to the pre-review are not returned to the IRB after 45 days, the submission will be administratively withdrawn, and the PI will be required to re-submit the study as an Initial application in the electronic IRB system.

B. Exempt Review

There are some categories of human subject research that are considered exempt from the regulatory requirements. As such, in accordance with federal regulations 45 CFR 46.104 and 21 CFR 56.104, research activities in which the only involvement of human subjects will be in one or more of the following categories can be determined to be exempt. It should be noted that an exempt determination does not mean human subjects are not involved. It means that the level of risk to the subjects is low enough to not require continued IRB oversight. Studies deemed to meet exempt category 2iii or category 3iC require a limited IRB review to ensure there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The IRB still reviews applications related to exempt research to ensure the research fulfills ethical standards, such as,

i. The research holds out no more than minimal risk to participants.
ii. The selection of participants is equitable.
iii. If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
iv. If there are interactions with participants, someone with appropriate qualifications and expertise should determine whether there should be a consent process that will disclose such information as:
    - That the activity involves research.
    - A description of the procedures.
    - That participation is voluntary.
    - Name and contact information for the researcher.
    - There are adequate provisions to maintain the privacy interests of participants.

Category 1: Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular

and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Category 2: Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

*Reminder: See the below restrictions regarding research in this category that involves children.

Category 3:

i. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

   A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

   B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

   C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

ii. Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met,

examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

iii. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that they will be unaware of or misled regarding the nature or purposes of the research.

Category 4: Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

i. The identifiable private information or identifiable biospecimens are publicly available;

ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

Category 5: Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under

contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

Category 6: Taste and food quality evaluation and consumer acceptance studies,

i. if wholesome foods without additives are consumed or

ii. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Categories 7 & 8: Not applicable at Lurie Children's as broad consent has not been adopted.

i. Exemptions from IRB review cannot be applied to research involving the following:

   a. Research in all categories that involves prisoners (per 45 CFR 46.46.301(a)).

   b. FDA-regulated research in categories 1-5 (per 21 CFR 56.104).

   c. Research that falls under category 2 and includes children as subjects, ***except*** for educational tests and projects involving the observation of public behavior and the investigators do not participate in the activities being observed. Exemption 3 does not apply to research involving children.

   d. Research in all categories that is greater than minimal risk.

ii. When considering applications for exemption from IRB review, ORIC staff completes a review of a proposed activity to ensure that the activity is conducted safely and ethically. Accordingly, each application for exemption is reviewed to ensure that the following protections are in place:

   a. A plan to minimize any potential risks to subjects;

   b. An appropriate consent process, if applicable; for example, a disclosure statement at the beginning of a survey;

   c. The process by which the privacy of subjects and the confidentiality of the research data will be maintained; and

   d. A plan for monitoring the safety and welfare of enrolled participants.

Upon receipt of the Initial application in the electronic IRB system, ORIC staff conducts an administrative and regulatory review of the application for completeness, and compliance with ORIC policies. The application is then reviewed by the IRB Chair or Vice Chair to determine if the protocol may be exempt according to the exemption categories outlined in 45 CFR 46.104. For studies that qualify for review under exempt categories (2)(iii) and (3)(i)(C), the application will be reviewed by the IRB Vice Chair under a limited IRB review. If an IRB member reviewing the research finds that research is greater than minimal risk, the reviewer must document the rationale for this determination and the rationale for review by the convened IRB.

Researchers must submit the following for studies qualifying for limited IRB review:

- The full protocol, application, or a protocol summary containing the relevant information to determine whether the proposed research fulfills the criteria for approval.
- The proposed consent document, if applicable.

IRB members conducting limited IRB review may not disapprove research, rather they ensure there are adequate protections for privacy interests of participants and the confidentiality of identifiable data when research falls under exempt category 2 and 3, and that exempt research under limited IRB review fulfills Lurie Children's ethical standards. Continuing review is not required for studies that qualify for limited review. Lurie Children's retains the authority to suspend or terminate IRB approval of research approved via limited review.

If the research is deemed to be exempt, a letter that documents this finding is sent to the PI. The letter documents the specific category under which the exemption is being granted.

Renewal reports are not required for exempt protocols; however, the PI is informed in the determination letter that any proposed changes to exempt human research must be submitted to ORIC, prior to implementation, in order to determine if the research still qualifies for exempt status. If the ORIC staff or IRB Chair/designee finds that the research is no longer eligible for exemption, the PI will be notified the study needs to be submitted for expedited or full board review by the IRB.

C. Full or Expedited Review

Submissions may be processed by expedited review or may require review at a convened meeting of the IRB. The preliminary determination of the type of review procedure is made by the ORIC staff and the IRB Chair based on the provisions of the federal regulations as defined in 45 CFR 46. The standard requirements for informed consent (or its waiver, alteration, or exceptions) apply regardless of the type of review – expedited or convened – utilized by the IRB.

When the study involves children, one of the following OHRP and FDA (if the study involves an investigational drug, biologic or device) risk categories will apply :

- OHRP 46.404/FDA 21 CFR50.51: Research not involving more than minimal risk.
- OHRP 46.405/FDA 21 CFR50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- OHRP 46.406/FDA 21 CFR50.53: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- OHRP 46.407/FDA 21 CFR50.54: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

D. Expedited Review

Federal regulations allow for IRB review of nine specific categories of research through expedited review procedures (45 CFR 46.110 and 21 CFR 56.110). To qualify for expedited review, research must involve no more than minimal risk to human subjects and involve only procedures listed in one or more of the expedited review categories listed in guidance issued by HHS and the FDA.

Regarding Initial applications and Renewals, the types of research that qualify for expedited review are those that involve no more than minimal risk per 45 CFR 46.110 and 21 CFR 50.110 and are found listed in the Notice published in the Federal Register. The IRB will use the expedited review procedure for all research protocols falling within these categories.

- Category 1: Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    - Research on drugs for which an investigational new drug application (IND) (21 CFR Part 312) is **not** required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
    - Research on medical devices for which (i) an investigational device exemption (IDE) application (21 CFR Part 812) is **not** required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or from other adults and children*, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

*Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a)

- Category 3: Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
    - hair and nail clippings in a non-disfiguring manner;
    - deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
    - permanent teeth if routine patient care indicates a need for extraction;
    - excreta and external secretions (including sweat);
    - uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
    - placenta removed at delivery;
    - amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
    - supra- and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
    - mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
    - sputum collected after saline mist nebulization.
- Category 4: Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:
    - physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
    - weighing or testing sensory acuity;
    - magnetic resonance imaging;
    - electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography;

- moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

- Category 5: Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)
- Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes
- Category 7: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.)
- Category 8: Continuing review of research previously approved by the convened IRB as follows:
    - Where the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or
    - Where no subjects have been enrolled and no additional risks have been identified; *or*
    - Where the remaining research activities are limited to data analysis.
- Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Once all issues noted by the RCC review have been addressed, a submission that qualifies for expedited review is forwarded to the IRB Chair or Vice-Chair or designated reviewer for review.

In reviewing the research, the designated reviewer(s) may exercise all authorities of the IRB except that the reviewer(s) may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in 45 CFR 46.108(b).

Applications that have been reviewed by the IRB at a convened meeting, and the IRB determined that the review of the PI's response is to be processed via expedited procedures, can include the following:

a. Minor, non-substantive modifications to the consent form(s), recruitment advertisements, and other study documents based on the IRB's request.
b. Minor, non-substantive modifications to the electronic IRB system application based on the IRB's request.
c. Acceptance of a PI's confirmatory response to the IRB's understanding or directive.

The IRB Chair has designated the IRB Vice-Chair(s) to use the expedited review procedures to perform the review of studies falling in the following categories:

i. Initial applications, Renewals, and Modifications to protocols that are no more that minimal risk and all study procedures meet the criteria in the 7 expedited categories described above and minor changes in previously approved research during the period for which approval is authorized (45 CFR 46.110, 21 CFR 50.110)
d.

ii. For review of Renewals that were initially reviewed by the IRB at a convened meeting that fall into one of the following categories:

a. Research permanently closed to the enrollment of new subjects. All subjects have completed all research-related interventions and the research remains active only for long-term follow up of subjects; or
b. Research in which the remaining activities are limited to data analysis only; or
c. Research where the fully convened IRB previously determined that future reviews may be conducted under Expedited Category #9, and where no significant modifications have been made in the previous year of approval.

iii. Study closeout applications.

iv. Review and acceptance of contingencies noted by the RCC and IRB during a previous review of a study.

v. Review of submissions that require acknowledgment:

a. Data Safety Monitoring Board/Committee (DSMB/C) reports

b. Investigator's drug (or device) brochures

c. Study closure memos (indicating temporary or permanent closure in subject enrollment)

d. Study reactivation memos (indicating reactivation of research procedures)

e. Package inserts for investigational drug/device

E. Administrative Review

The IRB Chair has delegated the authority to review and approve administrative modifications to the Office of Research Integrity and Compliance staff. These reviews include the following:

a. Modifications to study personnel

b. Minor non-substantive Modifications to study documents including but not limited to:

1. Changing a study title and/or funding source
2. Changing a telephone number
3. Deleting items from a questionnaire without material change to the study
4. Editorial revisions to the consent form(s), recruitment advertisements, and other study documents
5. Minor content revisions to IRB approved consent forms (such as minor grammar corrections, changes in contact information, department affiliation, or similar administrative revisions)
6. Administrative clarifications or edits to protocols or Investigator's Brochures that do not affect the risks to subjects

c. Submission of study or consent documents translated into a foreign language and the required translation certificate(s).

d. Submission of revised or additional recruitment materials, such as a flyer, for studies that are already approved to recruit subjects using recruitment flyers or advertisements.

F. Full Board Review

The IRB will conduct full committee review of all Initial applications that do not qualify for expedited review and are not found to be exempt from 45 CFR 46 and 21 CFR 56. The IRB meeting schedule will be posted on the IRB website. Typically, each committee convenes once a month. There is no limit to the number of studies considered at each meeting. Modifications to approved studies that represent more than minimal risk, more than a minor change in previously approved research, or an increase in risk of previously approved research also require full committee review. In addition, Renewals that do not qualify for expedited review (see above) will undergo full committee review no less than once per year. In some cases, the IRB may elect to review studies more often than once per year.

i. Approximately ten days prior to the IRB meeting, IRB member reviewer assignments will be made. In collaboration with the RCC, will finalize assignments of submissions to reviewers.

   a. For Initial applications, all documents submitted to the IRB (protocol, consent documents, recruitment materials, Investigator's Brochure, etc.) will be available for review by all members of the IRB (including alternate members) in the electronic IRB system. For all Initial applications, there will be a primary reviewer, a secondary reviewer, and a consent reviewer; they will present the Initial application and study documents to the IRB at the convened meeting. Although there is a separate consent reviewer, each reviewer will be asked to ensure that the consent documents are appropriate. In addition, the reviewers will have access in the electronic IRB system to review the respective division head and department chair sign-off and verification that the PI is qualified to conduct the research.

b. For Renewals and Modifications that require convened IRB review, the protocol or research plan (protocol summary, if applicable), current consents, proposed consents, and status report that includes the elements described above, will be made available in the electronic IRB system for review by all members (including alternate members). For Renewals and Modifications, one primary reviewer will be assigned to present the submission to the IRB at the convened meeting.

ii. To ensure that an appropriate scientific review is being done, Initial applications will be assigned to reviewers based on each reviewer's area of expertise. If it is determined that consultants or experts will be required to advise the IRB in its review of an Initial application, the Initial application and study documents will also be distributed to the consultant(s) or expert(s) prior to the meeting. However, these individuals may not vote on motions made by the convened IRB.

iii. Applications, including all submitted study documents, scheduled for review at a convened meeting will be distributed via Electronic IRB system to all IRB members at least one week prior to the meeting (preferably 10 days prior). The IRB Chair or designee may make an exception and distribute an item to a designated reviewer(s) after this time if an item requiring urgent review is submitted to the IRB after the submissions have been distributed.

iv. A majority of the membership of the IRB constitutes a quorum and is required in order to convene a meeting for the review of electronic IRB system applications.

v. For approval of all reviews of research including Initial applications, Renewals, and Modifications, the IRB will use the required approval criteria as outlined by 45 CFR 46.111 and 21 CFR 56.111.

vi. To be approved, the review has to receive the approval of a majority of the members present at the meeting.

vii. An IRB member whose concerns are primarily in non-scientific areas must be present at the convened meeting before the IRB can conduct its review of research.

viii. The minutes for the convened meeting includes a review of any studies that were approved during the prior month via expedited review (Initial applications, Renewals, and/or Modifications), exempt studies, adverse events/unanticipated problems, reviews of studies that rely on external IRBs, and Closures.

ix. No IRB member may participate in the committee's review of any research in which that member has a conflict of interest (COI), except to provide information requested by the IRB.

a. The Chair will act as a regular voting member and will not routinely abstain on all votes, unless named as a co-investigator or because of another COI.

b. Other IRB members will not routinely abstain on votes on studies that originate from their own Divisions or Departments, unless named as a co-investigator or because of another COI.

c. An IRB Member who is PI of a study being reviewed, if they are present at the time the study is discussed, may remain in the room for the discussion and vote but may not provide any information unless directly asked. The IRB Member will then be recused from the vote. It will be duly noted in the minutes, if at the time their study was discussed, the IRB Member was not present in the room and therefore not counted in the vote tally.

x. To facilitate the review of research and the protection of the rights and welfare of human subjects, the PI may be contacted by the IRB to answer any questions that the board thinks the PI may be able to resolve prior to the IRB's deliberation and vote. The PI may be contacted by phone during a meeting or asked to attend a portion of the meeting in order to answer the IRBs directed questions. After answering any directed questions, the PI will be dismissed and will not be present during the discussion and vote by the IRB.

xi. Alternatively, the IRB Chair or other designated member(s) of the IRB may schedule to speak with the PI prior to the planned prior to the meeting to talk with the PI about various issues/concerns related to their study under review.

xii. Unless invited by the IRB or an IRB Member, it is not standard practice for research investigators to be contacted during the IRB meeting where their study is being reviewed by the convened IRB.

xiii. Renewals of studies previously reviewed by the convened IRB that fall into one of the following categories must undergo convened IRB review:

- Actively enrolling new participants and/or providing research-related interventions to previously enrolled subjects.
- Subject accrual completed, however, previously enrolled subjects continuing to receive research-related interventions.

G. IRB Notifications and Approvals

i. The IRB will notify the PI in writing of the reasons for the committee's decisions, conditions, and requirements. The IRB will keep track of the PI's response, and an approval letter will not be issued until all outstanding issues are addressed and reviewed by the convened IRB (when appropriate).

ii. A copy of the IRB meeting minutes can be made available to representatives of the Institution, including the Chief Medical Officer and Sr. Vice President and Chief Operating Officer of the Research Center to review.

iii. For Initial applications and Renewals that require full Board review, the approval period expires on the last day of the month prior to the anniversary of approval. However, the approval period may be shorter than one year at the discretion of the IRB as directed by the degree of risk. If the IRB determines that a project would require review more often than once per year, the reasons for this will be documented.

iv. The following categories will be used to designate the status of the application upon review:

a. Approval

If the IRB is satisfied with the application in the electronic IRB system in its current form, the IRB can approve the study. As with all submissions, investigators cannot begin any study activities until they are in receipt of the formal letter of IRB approval and stamped consent documents (when applicable). For Modifications, no change to the protocol may be implemented until the investigators have received an IRB approval letter for the change (except in emergency situations).

b. Approval with minor directed contingencies

In many instances, approval is given with minor directed contingencies, which can include questions from the IRB reviewer(s) and/or requests to make changes to the application and/or consent form(s).

The IRB may approve a study with minor directed contingencies if the changes it requests are not substantive, such as editorial revisions in the consent form. Review and approval of the PI's response to the IRB's contingencies can typically be performed by the IRB Chair, or their designee, via an expedited procedure. However, the Chair or designee may send the PI's response back to the convened IRB if they feel the response requires review by the convened IRB.

Investigators cannot begin any study activities until they are in receipt of the formal letter of IRB approval and stamped consent documents (when applicable). For Modifications, no change to the protocol may be implemented until the investigators have received an IRB approval letter for the change (except in emergency situations. If responses to contingencies on Initial applications are not returned to the IRB after 45 days, the submission may be administratively withdrawn and the PI will be required to re-submit the study as an Initial application in the electronic IRB system.

If a Renewal or Modification is approved with minor directed contingencies and the study expires before these contingencies are reviewed and approved, all research activities must stop until approval is obtained.

c. Deferred (tabled)

In this case, the IRB feels the application does not provide sufficient information to make a determination, including a risk determination, as to whether the proposed research meets the criteria for IRB approval and sufficient problems exist that the PI must address. The IRB will provide the PI with its critique. Unlike contingent approvals, the response to the deferral issues must be reviewed by the convened IRB.

d. Disapproval

In this case, the IRB feels the research does not adequately protect the interests of proposed subjects. When a research protocol has been disapproved, the IRB Chair will provide the PI with the reasons for the decision to disapprove and the written meeting minutes. The PI may appeal the IRB's decision. However, the IRB will only reconsider a rejected protocol after the PI modifies the protocol to address

satisfactorily the committee's objections. The IRB can make the same determination for a Modification to a current study.

vii. For Initial applications and Renewals that require full board review, the IRB may approve the study for a period of no more than one year. Typically, the approval period expires on the last day of the month prior to the anniversary of approval. However, the IRB may shorten the approval period and require more frequent periodic review as is appropriate to the degree of risk of the study. However, if a protocol is approved with directed contingencies, the start date of the approval period will not begin until the contingencies are lifted and the IRB Chair or designee approves the response. The approval period will end on the last day of the month prior to the anniversary of the meeting at which it was discussed.

viii. It is important to note that the approval period for any study may be shortened at the discretion of the IRB. For example, an investigator may be asked to submit a Renewal within a shorter period if the IRB has concerns about an approved research protocol.

H. IRB Deferral Conference Call Meeting

When the convened IRB votes to defer a protocol, the PI's response requires review by the convened IRB, either at future convened IRB meetings, or in special circumstances, at a meeting held via conference call. The opportunity to submit the requested revisions to the IRB for the review at an IRB Deferral Conference Call Meeting that occurs between the monthly board meetings is offered under circumstances when it is not in the best interest of potential subjects to delay the start of the study a full month for the next in-person convened IRB meeting or at the discretion of the convened IRB at the time the deferral motion is passed.

The IRB Deferral Conference Call Meeting is in a conference call format and requires a quorum of members. It takes place after the Initial Application was reviewed by the convened IRB, and prior to the next scheduled IRB full board meeting. The PI must provide to the IRB responses addressing all items from the initial meeting review. The criteria for placement on the agenda of the IRB Deferral Conference Call Meeting is that there are no outstanding items, including those considered administrative in nature.

I. IRB Authorization Agreement

An IRB Authorization Agreement is a written agreement between two institutions engaged in human subjects research when establishing single IRB review. This agreement outlines the roles and responsibilities of each institution: the institution ceding review and the institution serving as the reviewing IRB of record including:

- The process for the reviewing IRB to obtain conflict of interest management plans.
- Reporting requirements and timelines for possible unanticipated problems, participant complaints, protocol deviations, and other events, so the IRB obtains information necessary to make required determinations for unanticipated problems involving risks to participants or others.
- The process for the IRB to communicate suspension or termination of IRB approval to the researcher and researcher's organization.
- How the IRB will notify the researcher, and if applicable the researcher's organization, of its decisions.

- How the IRB will make available relevant IRB records, including but not limited to minutes, approved protocols, consent documents, and other records that document the IRB's determinations to the relying organization upon request.
- How the IRB will provide relevant policies to the relying organization, including HRPP staff, and researchers and research staff, and the mechanism for communicating to the organization when policies are updated, as appropriate.
- How researchers can contact the IRB, by providing contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the IRB.
- When sharing oversight of research, a written agreement or policies and procedures must describe the respective responsibilities of each organization.
- A description of which institution is responsible for providing education to researchers and research staff.
- A description of which institutions conducts scientific review.
- Ensuring concordance between any applicable grant and the IRB application.
- Reviewing potential non-compliance, including complaints, protocol deviations, and results of audits:
    - Identifying which organization is responsible for deciding whether each allegation of noncompliance has a basis in fact.
    - Identifying which organization's process is used to decide whether each incident of noncompliance is serious or continuing.
    - Obtaining management plans for researcher and research staff conflicts of interest. If the relying organization maintains responsibility for this issue, the management plan must be provided to the IRB in a timely manner prior to the decision by the IRB.
- Managing organizational conflict of interest related to the research.
- Ensuring that, should termination of a reliance agreement occur, one of the parties clearly is responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the studies.

J. Acceptance of External IRB Review

i. When our Institution will Rely on the Review of an External/Central IRB

Human subjects research conducted at the Institution must be reviewed and approved by the Lurie Children's IRB, which exceeds the federal requirements for composition and has the requisite scientific expertise from various disciplines to ensure the protection of the vulnerable population we serve.

Reliance on an external (outside) IRB is permissible under 45 CFR46.114 and will be considered by the IRB Chair or designee on a case-by-case basis only for cooperative research projects where the reviewing IRB has the requisite knowledge and expertise. Cooperative research projects include those where more than one institution is engaged in federally-funded human subjects research activities. Often a specialized central IRB has been established for sole purpose of reviewing a category of investigative studies (e.g., the NCI CIRB) or the cooperative study group has designated an IRB to serve as the IRB of record for a study or group of studies. For the Institution to consider reliance

on an external IRB, the reviewing IRB must hold an FWA issued by OHRP, hold the appropriate accreditation (i.e., AAHRPP), have the requisite composition, and have the specialized scientific expertise for the type of study(ies) to be reviewed. Likewise, the Lurie Children's IRB may serve as the IRB of Record for a relying institution (e.g., when a Lurie Children's PI is the lead PI for a multi-center study or other compelling circumstances).

In order for such a reliance to be implemented, the Lurie Children's IRB must enter into an IRB Authorization Agreement (IAA) with the qualified external IRB. The IAA (reliance or cooperative agreement) defines the terms, scope and limits, and roles and responsibilities of the joint review arrangement and must be signed by the Institutional Official of each institution involved. Negotiating such an agreement can be quite involved and often times may take much longer than local IRB review which is taken into consideration. This agreement must be kept on file at both institutions/organizations and made available upon request to OHRP or any U.S. federal department or agency conducting or supporting research to which the FWA applies. An IAA may be developed on a case-by-case basis for a single study or apply to multiple studies between the institutions. Each institution is still responsible for safeguarding the rights and welfare of human subjects. Investigators who wish to request reliance on an external IRB must contact ORIC staff and provide justification for the use of an external IRB.

Proper documentation must be provided in the electronic IRB system abbreviated application for reliance along with 1) the executed reliance agreement between the institutions; 2) a copy of the initial approval letter from the IRB of record; 3) a copy of the protocol; 4) a copy of the informed consent document(s) and any recruitment materials that will be used at the Institution; and 5) other study materials as applicable (e.g., Investigator's Brochure). The local IRB may request more information as needed (i.e., IRB composition, meeting minutes, etc.). The consent forms and recruitment documents must be modified to meet the Institution's template requirements.

This facilitated/expedited internal review serves to ensure:

- The proposed protocol adheres to the Institutional requirements for ensuring the protection of human subjects;
- The Institution has adequate facilities and staffing to carry out the proposed research;
- The proposed consent form includes language that addresses Institutional policy and requirements;
- An appropriate assent process will be followed (where applicable, the facilitated/expedited reviewer will approve an assent document to be used during the conduct of the research); and
- An appropriate Authorization for the use of PHI in a research setting is issued.

Renewals of protocols originally reviewed and approved under a reciprocal agreement may be reviewed via facilitated/expedited review (i.e. reliance on the external IRB).

The objectives of facilitated/expedited Renewal mirror those for Renewals completed by the IRB. The IRB Chair, Vice-Chair(s), or designee, are responsible for ensuring that the study continues to meet the requirements for the protection of human subjects. PIs are required to submit Modifications and adverse events to the IRB, and the IRB Chair or Vice-Chair(s) must have access to a summary of all Modifications and safety or other reports. Upon approval, the consent, assent, recruitment documents, and HIPAA authorization form (if any) are re-issued for use within the Institution.

a. NCI CIRB:

The National Cancer Institute Central IRB (NCI CIRB) has adopted an independent model in which they are the sole IRB of record responsible for both the study review as well as the review of local context considerations.

i. Local Context Considerations

In the independent model, the NCI CIRB requires information describing local context considerations. Our local context considerations are identified and reported to the NCI CIRB via annual and study-specific worksheets and include: state and local laws, conflict of interest policies, boilerplate language for inclusion in the consent document, and any other Institutional requirements. Local context considerations for investigators include: resources available to support research, extent of existing research responsibilities, informed consent process information, including descriptions of vulnerable populations eligible for enrollment and safeguards used to protect those populations. Privacy and confidentiality protections, in addition to any unique study-specific considerations, are also reviewed by the NCI CIRB as part of local context.

ii. Two Key Local Responsibilities

The Institution has the responsibility to report to the NCI CIRB potential unanticipated problems or serious or continuing noncompliance. The NCI CIRB reviews, makes a final determination, and reports to the Federal regulatory agencies, if necessary.

The local PI has the responsibility of merging the NCI CIRB-approved local boilerplate text into the NCI CIRB-approved consent document. No further NCI CIRB review is required because both components are already NCI CIRB-approved.

iii. Process for Submission

Once the Institution has executed the Authorization Agreement/Division of Responsibilities agreement with the NCI CIRB, the following will be operative at the Institution:

a. New protocols will be presented and reviewed at the disease-specific team meeting in the Division of Oncology. If it there is a consensus to participate, the protocol will be presented and reviewed at the Oncology Research Meeting. At this meeting, decision will be

rendered whether a NCI CIRB approved protocol should be activated at the Institution and the PI, a Children's Oncology Group (COG) member, will be confirmed. That PI forwards a copy of the protocol, the study specific NCI CIRB approved consent documents, and the meeting minutes from the NCI CIRB review via the electronic IRB system. The IRB Chair, a Vice-Chair, or Acting Chair will decide on a protocol-by-protocol basis whether to agree to accept the NCI CIRB independent review oversight of the study or to conduct its own local IRB convened review.

b. If the decision is made to accept NCI CIRB independent review oversight of a particular protocol at our Institution, the PI on behalf of the Institution is responsible for ensuring the safe and appropriate performance of the research at the Institution as follows:

    - Complying with the NCI CIRB's requirements and directives;
    - Ensuring the safe and appropriate performance of the research, including the following:
        - ensuring the initial and ongoing qualifications of investigators and research staff;
        - overseeing the conduct of the research;
        - monitoring protocol compliance;
        - maintaining compliance with state, local, or Institutional requirements related to the protection of human subjects;
        - providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research; and
        - investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing noncompliance. When notifying the NCI CIRB of a potential unanticipated problem and/or serious or continuing noncompliance, the Institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences. In addition, as part of ensuring safe and appropriate performance of research, the Institution has the authority to observe any aspect of the research process including observing the consent process. The NCI CIRB

retains the authority to direct this to be done when necessary.

- Providing updates in a timely manner to the NCI CIRB whenever an Institutional Principal Investigator is no longer the responsible party for a study under the purview of the NCI CIRB;
- Notifying the NCI CIRB when a regulatory deficiency has been cited on an institutional COG audit that occurred during the time that the NCI CIRB was responsible for study review;
- The PI is responsible for completing and submitting all documents to the NCI CIRB and ensuring the local IRB is copied, including, but not limited to:
    - the Annual Institution Worksheet About Local Context (local IRB approval required before submission);
    - the Annual Investigator Worksheet About Local Context;
    - the Study-Specific Worksheet about Local Context (local IRB review required before submission);
    - the local consent form:
    - incorporating NCI CIRB-approved boilerplate language into the NCI CIRB-approved model consent form (local HIPAA language, etc.);
    - making no language changes to the consent form with the exception of NCI CIRB-approved boilerplate language;
    - obtaining NCI CIRB approval of changes to the boilerplate language prior to implementation; and
    - obtaining NCI CIRB approval of translations of the consent form prior to implementation; and
    - any other worksheets/forms required by the NCI CIRB for participation.
- Maintaining a regulatory file for each study under NCI CIRB purview as per local institution and sponsor policy.

ii. When external IRBs Rely on the Review by Lurie Children's IRB

In an effort to facilitate the review of research and support of those investigators who conduct research activities involving our Institution and others, the Lurie Children's

IRB may serve as the IRB of Record. The decision to be the IRB of Record will be made on a case-by-case basis.

IRB applications or other materials contain a description of any laws relevant to the study being reviewed by the IRB, when research is conducted in another state or country. Information about relevant laws may be provided in a memorandum of understanding, research site agreement, local context form, or other ways.

The IRB will review requests to add research sites to previously approved protocols when submitted to the IRB as Modification. When the request is limited to adding a US site at an institution with an approved FWA, the request will be reviewed/approved by the expedited review pathway. When the request adds an international site and/or is accompanied by extensive protocol changes, the Modification will be reviewed by the convened board that may request submission of a separate detailed protocol.

i. Ensuring concordance between any applicable grant and the IRB application.
ii. Reviewing potential non-compliance, including complaints, protocol deviations, and results of audits:
    - Identifying which organization is responsible for deciding whether each allegation of noncompliance has a basis in fact.
    - Identifying which organization's process is used to decide whether each incident of noncompliance is serious or continuing.
    - Obtaining management plans for researcher and research staff conflicts of interest. If the relying organization maintains responsibility for this issue, the management plan must be provided to the IRB in a timely manner prior to the decision by the IRB.
iii. Managing organizational conflict of interest related to the research.
iv. Ensuring that, should termination of a reliance agreement occur, one of the parties clearly is responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the studies.

a. Lurie Children's/Northwestern University Reliance Agreement

For the review of research involving the Institution and Northwestern University (NU) and/or an NU Affiliate (NMH, CDH, RIC, etc.), investigators may request that the Lurie Children's IRB serve as the IRB of record for NU or an NU affiliate under this reliance agreement. The agreement is in accordance with OHRP requirements and guidelines and defines the relationship between the IRBs and the responsibilities of each institution. The Lurie Children's IRB reviews studies that involve research activity at both NU and the Institution or faculty of both institutions, and/or funding through NU with activity at the Institution.

b. Process for Submission

- The PI, from either institution, will submit the study via the electronic IRB system indicating the nature of involvement of NU and/or requesting the Lurie Children's IRB to serve as the IRB of Record.
- The study will be routed for review by the Lurie Children's IRB. ORIC staff will issue the review determination/approval documents to the PI via the electronic IRB system.
- The PI will submit the study into the NU eIRB+ system indicating intent to rely on an external/central IRB.
- The PI uploads the Lurie Children's IRB review determination/approval into NU eIRB+.
- Subsequent submissions (Renewals, Modifications, etc.) are to be submitted via the electronic IRB system for review. The PI is responsible for providing NU with any amended/approved documents and approvals.

K. Protecting the Safety and Welfare of Participants Enrolled in an Expired Protocol

If continuing approval is not issued prior to the protocol's expiration date, the electronic IRB system will send a *Protocol Expiration Notice* to the PI of the expired study requiring that all human research activity, including data analysis, cease until further notice.

In the event that a protocol's approval expires but the withdrawal of research interventions may place subjects of the study at risk, the PI may continue with protocol-specific interventions that relate to subject safety only; for example continuing to provide the investigational agent and continuing procedures for monitoring of adverse events. Ongoing recruitment and enrollment, data analysis, and ancillary research activities not related to subject safety (e.g. study questionnaires, research-only blood draws for optional studies, etc.) must end until continuing approval has been granted.

Within the Renewal submission in the electronic IRB system, the PI is to provide a current status of the study and subjects that details the following:

i. An explanation of why the submission of the Renewal was delayed;

ii. A discussion of why the suspension of research activities would adversely impact subject safety or go against the subjects' best clinical interest;

iii. A description of all research-related procedures performed on each subject post-expiration and how each relates to subject safety; and

iv. A plan to prevent such lapses of approval in the future.

If any unanticipated problems or serious adverse events occur during the lapse in IRB approval, the PI must submit an Incident Report in Cayuse immediately following the approval of the Renewal.

L. Reactivation of Protocols When Previous Approval Has Lapsed

As noted previously, it is the PIs responsibility to ensure that a request for continuing approval is submitted and approved before the study's current expiration date. It is noted, however, that in some cases a lapse in IRB approval may occur.

Investigators are prohibited from performing any research-related activities, including data analysis, after a study's expiration date, unless for reasons of subject safety and welfare.

A Renewal application for an expired protocol is to be submitted and should include the following:

i. Verification that no study related activities occurred from the date of expiration to the present, including any activities related to the survivorship tracking of previously enrolled patients and data analysis;

ii. A statement as to whether any new subjects were enrolled in this study after the date of expiration;

iii. Discussion as to why continuing approval or a request to close was not previously submitted for this protocol; and

iv. An assurance that this, and all other protocols under the PIs supervision, will be submitted for continuing approval to ensure re-approval before the protocol's expiration date.

If, for any reason, the protocol has been without IRB approval for more than 45 days, the protocol may be administratively closed the PI will be required to re-submit the study as an Initial application in the electronic IRB system.

M. Type of Review for Modifications

IRB review of an amended submission focuses on the effect of proposed changes on human subjects, specifically to determine whether the changes pose additional risk to subjects or represents a significant change in study procedures.

Modification applications may receive full Board or expedited, according to the nature of the proposed changes and their effect on the risk/benefit ratio.

If the changes proposed to a protocol that presents more than minimal risk to subjects are substantial, in that they include modifications that differ significantly from the previously approved protocol, or if they alter the risk/benefit ratio of the study, then the Modification must be reviewed by the convened IRB. Such Modifications should be incorporated as part of a revised protocol. Examples of such changes are an increase in dosage of an investigational drug, addition of procedures that increase risk to subjects (e.g., addition of a PET scan), addition of a new subject population (e.g., broadening the eligibility criteria to include children), and significant change in study design.

If the proposed changes to the protocol are minor, the Modifications may qualify for expedited review. A minor Modification is defined as any change in the previously approved protocol that does not deviate significantly from the requirements for approval imposed during the previous IRB review. Examples of changes that may qualify for expedited review are: editorial changes to the protocol or consent form, minor changes to the informed consent document language, and addition of a procedure that does not pose more than minimal risk to study participants (e.g., the addition of a small volume blood draw).

Per the agreements that have been executed with the Institution and an external IRB of record, the IRB of record is responsible for reviewing and approving any modifications to previously

approved protocols. The PI notifies the IRB of any approved modifications by submitting a Modification application via the electronic IRB system along with the supporting documents and approval letter of the IRB of record.

During the review of external IRB approved Modifications, the IRB reviewer is responsible for ensuring that the proposed modification does not affect the safety and welfare of individuals enrolled at the Institution. The reviewer is also responsible for authorizing the use of any revised consent or recruitment documents.

N. Investigator Responses to ORIC Staff and IRB Correspondence

During the ORIC and IRB review processes, all requests for modifications or further clarifications are detailed to the PI in correspondence. The PI's response to correspondence must be evaluated in accordance with the requirement set forth during the initial review (i.e., returned to the convened Board or returned to the IRB Chair or Vice-Chairs, or a designated reviewer).

O. Approval Periods

The federal regulations state that an IRB can approve research for a period of no more than one year. It is important to note that the approval period for any study may be shortened at the discretion of the IRB. For example, an investigator may be asked to submit a Renewal within a shorter period if the IRB has concerns about an approved research protocol or the risks to subjects.