11.1 INFORMED CONSENT

A. Introduction and Description of Informed Consent

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many ethical prescriptions and evaluations of human actions. Three basic principles are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence, and justice. Respect for persons incorporates at least two ethical convictions: first, individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. Therefore, informed consent is a critical component of research. Informed consent is an ongoing process and not just a piece of paper or a discrete moment in time. Informed consent assures that research subjects will understand the nature of the research and can knowledgeably, and *voluntarily*, decide whether or not to participate.

B. Written Informed Consent and HIPAA Authorization Overview

Research investigators are responsible for obtaining informed consent in accordance with 45 CFR 46.116 and 21 CFR 50.20 to ensure that no human subjects will be involved in the research prior to obtaining legally effective informed consent. Unless otherwise authorized by the IRB, research investigators are responsible for ensuring that legally effective informed consent will:

i. be obtained from the subject or the subject's legally authorized representative (LAR); *and*

i. be in language understandable to the subject or the representative; *and*

ii. be obtained under circumstances that offer the subject or the representative sufficient opportunity to consider whether the subjects should or should not participate and that minimizes the possibility of coercion or undue influence; *and*

iii. not include exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the research investigator, the sponsor, the Institution, or its agents from liability for negligence; *and*

iv. include the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information; *and*

v. begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research; *and*

vi. present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject’s or legally authorized representative’s understanding of the reasons why one might or might not want to participate.

In addition, investigators are responsible to obtain an individual's signed permission to allow the use or disclose the individual's protected health information (PHI) for research purposes in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule for research (45 CFR 160 and 164). PHI includes all "individually identifiable health information," including demographic data, that relates to the individual's past, present or future physical or mental health or condition, the provision of health care to the individual, or the past, present, or future payment for the provision of health care to the individual, and that identifies the individual or for which there is a reasonable basis to believe it can be used to identify the individual. Individually identifiable health information includes many common identifiers (e.g., name, address, birth date, Social Security Number) and the full list of PHI identifiers can be found in Section 5: Investigator Responsibilities.

C. Individuals Who May Obtain Consent

Only members of the research team who are knowledgeable in all elements of the study can obtain consent as they can provide a complete and accurate description of the research and be prepared to answer questions about risks, benefits, and alternatives to participation. If the PI determines it is appropriate, he/she may delegate this responsibility to another investigator or study team member. When the PI is also involved in the care of the patient, it might be more appropriate to have another member of the study team obtain consent to avoid any potential conflict of interest/undue influence. The PI must indicate, in Cayuse IRB, which study personnel have been properly trained and delegated the authority and responsibility to obtain consent.

D. Individuals Who May Sign the Consent Document

Federal regulations require that legally effective (signed) informed consent be obtained from a subject or the subject's legally authorized representative (LAR). The informed consent of each subject must be documented with a written consent form signed and dated by the subject or his/her LAR prior to enrollment (45 CFR 46.117(a) and 21 CFR 50.27(a)). In certain circumstances, the requirement for obtaining a signed consent document may be waived by the IRB.

The PI or designee that has obtained consent is also required to sign and date the study consent form for each subject to attest to the following:

i. All the elements of informed consent described in the study consent form have been discussed fully in non-technical terms with the subject/LAR

ii. All questions asked by the subject/LAR were answered to the best of his/her knowledge

In some cases, the IRB may require that an additional witness to the consent process, other than the PI or study team member that is obtaining consent, also sign the consent form (e.g., when consenting a non-English speaking subject with a translated short form and an interpreter).

E. Timing for Informed Consent

Informed consent is only valid if it is voluntary in nature. Therefore, it is important to conduct the consent process in such a way that the potential subject does not experience coercion or undue influence. When possible, an investigator should not ask subjects to provide consent

when they are under stress or in compromised positions (as is often the case in clinical settings) but should seek alternative times to recruit and consent eligible subjects.

The IRB requires that potential research subjects be given sufficient time to thoughtfully consider their participation in a research study before they are asked to sign and date the consent form. The amount of time that is appropriate varies depending upon the nature of the research (including the severity of the illness for which any research intervention is contemplated), but the IRB encourages the practice of allowing potential subjects to take the consent form home with them to consider their participation in a stress-free environment in consultation with family and friends.

In research protocols where medical treatment and experimental procedures may overlap, the IRB may impose additional requirements to address any potential for misunderstanding on the part of the subject. The IRB may require that the timing of the informed consent process be such that all clinical options are outlined before the possibility for research participation is introduced. Such a requirement is intended to distinguish clearly between procedures conducted as part of standard care and those procedures related to the research.

F. Requirements to Document Informed Consent

The PI or designee obtaining consent should document the consent process in the subject's medical record or study file as applicable. This documentation should include: verification that the study was explained to the subject, parent/guardian, and/or LAR; that adequate time was given for them to review the consent; that all questions were answered; that consent/assent was obtained prior to any study related procedures (including drug washouts); and any other specifics of the consent process (i.e. if an interpreter and short form were used, if consent was obtained over the phone and why, etc.).

The PI or designee who has explained the study and obtained consent from the subject/LAR must sign the consent form. This is typically done immediately after the subject/LAR signs the consent on the same day. The PI's or designee's signature cannot pre-date the subject's/LAR's signature. The subject/LAR should always be provided with a copy of the consent form to use as continual reference for items such as scheduling of procedures and for emergency contact information.

A copy of the signed informed consent form is to be kept in the subject's medical record if clinically relevant. Clinically relevant refers to any study in which there could be clinical implications for the participant, this includes but may not be limited to any study that involves investigational drugs, devices, or biologics. This ensures the safety of patients who participate in research involving procedures or interventions, which may affect their clinical care management. If the subject does not have a hospital medical record, the original signed consent form is to be kept in the PI's research file.

The IRB has the right to examine the signed informed consent documents for subjects enrolled in a research study and the right to monitor the informed consent process at any time.

NOTE: Prior to January 1, 2014, when someone other than the PI obtained informed consent, the Lurie Children's IRB required the PI to sign the consent form as acknowledgment. The Lurie Children's IRB dropped this requirement effective January 2, 2014. However, PIs are still required to co-sign consents previously approved that contain the separate PI signature line (until these are amended and approved accordingly).

G. Posting of Clinical Trial Consent Forms

For new clinical trials conducted or supported by a Federal department or agency approved on or after January 21, 2019, 45 CFR 46.116(h) now require investigators to publicly post consent forms.

For each clinical trial, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal website that will be established as a repository for such informed consent forms.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g. confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

H. Elements of Informed Consent and HIPAA Authorization

Federal regulations define basic elements of informed consent which must be included in the written consent form and addressed in the consent process (45 CFR 46.116 and 21 CFR 50.25). They further describe additional elements to be included in the consent process where relevant and appropriate. All of the below elements of informed consent are included in the consent form templates provided by the IRB.

The basic elements of informed consent are:

- A statement that the study involves research; an explanation of the purposes of the research and the expected duration of the subject's participation; a description of the procedures to be followed, and identification of any procedures that are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subjects;
- A description of any benefits to the subject or to others that may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality or records identifying the subject will be maintained;
- For research involving more than minimal risk, an explanation as to whether any compensation is available and/or an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of and where further information about them may be obtained (see below);

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject;
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject would be otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- For new studies approved on or after January 19, 2018, the following element must be included: One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
    i. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
    ii. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

The additional elements of informed consent are listed below.

i. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;

ii. Anticipated circumstances for which the subject's participation may be terminated by the research investigator without regard to the subject's or the legally authorized representative's consent;

iii. Any additional costs to the subject that may result from participation in the research;

iv. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

v. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

vi. The approximate number of subjects involved in the study at all study sites;

vii. There is a statement that the results of the research will be posted on clinicaltrials.gov (when applicable): "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

viii. For new studies approved on or after January 19, 2018, the following element additional elements must be included, as applicable per study:

- A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
- For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

The IRB will determine if/when any/all of the following will be disclosed in the informed consent:

- The probability for random assignment to each treatment.
- The participant's responsibilities.
- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks.
- When applicable, the reasonably foreseeable risks or inconveniences to an embryo, fetus, or nursing infant.
- The important potential benefits and risks of the alternative procedures or courses of treatment that may be available to the participant.
- When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- A statement that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the participant's original medical records for verification of clinical trial procedures and data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally authorized representative is authorizing such access.
- A statement that if the results of the trial are published, the participant's identity will remain confidential.

An approval stamp will be affixed to versions of the consent forms reviewed and approved by the IRB.

In addition to the above, the HIPAA Privacy Rule requires the following elements to be included in the authorization for the use and disclosure of protected health information (PHI) for research purposes:

- Description of protected health information (PHI) to be used or disclosed (outlining the information in a specific and meaningful manner);
- Specific identification of person(s) or class of persons authorized to make the requested use or disclosure;
- The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure;
- Description of each purpose of the requested use or disclosure;

- An expiration date/expiration event that relates to the purpose of the use or disclosure ("end of research study" or "indefinitely" is permissible);
- A statement to indicate an individual's right to revoke his/her authorization in writing and the exceptions to the right to revoke and a description of how the individual may revoke authorization;
- A statement identifying the consequences of refusing to sign the authorization; and
- The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement may be a general statement that the Privacy Rule may no longer protect health information.

An impartial witness should be present when obtaining consent from a subject/LAR that is unable to read. After the written consent document and any other written information to be provided to subjects, is read and explained to the subject/LAR, and after the subject/LAR has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign the consent document. By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject/LAR, and that consent was freely given by the subject/LAR.

It is imperative that the consent form be written in language that all potential participants can understand, so they can make an informed decision regarding participation in the research. To this end, the IRB requires that consent forms be written in non-technical, lay language at or below an eighth-grade reading level.

I. Requirements for Research-Related Injury Statements in Consent Forms

The federal requirements mandate that "for research involving more than minimal risk, an explanation as to whether any compensation is available and/or an explanation as to whether any medical treatments are available if injury occurs is a required element of informed consent."

The IRB has adopted uniform consent template language which is consistent with this requirement and the Office of Sponsored Programs' policy on Research Related Injuries for Industry Sponsored Clinical Studies. Consent forms for more than minimal risk studies are required to contain the following paragraph:

> *Contact the study doctor as soon as possible, if your child is injured while taking part in this study. Lurie Children's will assist you in finding medical care if needed. You or your insurer may be billed for such treatment.*

Additional wording which may be included when applicable:

> *The sponsor, (Sponsor name), will pay for medical expenses related to an injury caused as direct result of taking part in this study. For example, if the injury is from the study drug or a study procedure. They will not pay for medical expenses related to a pre-existing or underlying condition or the normal progression of a disease or treatment of a disease.*

J. Return of Research Results or Incidental/Secondary Findings to Participants

Knowing whether or not research results will be returned to participants may be an important piece of information in participants' decision of whether to participate in the research study. If investigators will be returning research results or incidental/secondary findings, this plan is to be included in the Cayuse IRB Initial Application and described in the consent forms.

Currently, there is no consensus on what types of incidental and secondary research results should be returned to participants. The National Bioethics Advisory Committee states that findings are to be returned to participants if (a) "the findings are scientifically valid and confirmed" (b) "the findings have significant implications for the subjects' health concerns" and (c) "a course of action to ameliorate or treat these concerns is readily available."

When research-related test results are returned as a part of the study, these are to be validated in a CLIA-certified lab prior to returning any results to a participant and/or family member.

Investigators are to consider the following when planning to return research results to participants:

- Whether individual or summary-level (aggregate) results will be returned, and if so, what types of findings may be returned. Including if this return of information is optional.
- When and how results will be returned to participants, including thoughtful consideration of whether, when, and how to incorporate participant preferences.
- A plan for the incorporation of outside expertise, if necessary, to evaluate or return incidental findings.
- Whether results may be returned by secondary investigators if samples or data are deposited in a biobank or data repository.
- Whether participants may receive unanticipated incidental findings, including lifesaving incidental findings.
- A clear outline of what follow-up assistance will be provided to participants, if applicable.

K. Observation of the Consent Process and the Research

ORIC has the authority to observe or have a third party observe the consent process and the conduct of the research. ORIC also has the discretion of appointing an ombudsman to oversee the research process in cases where the subject is particularly vulnerable.

i. Ombudsman

The IRB Chair, Vice-Chair(s), or convened IRB may appoint an unbiased individual to act as a subject advocate or a liaison between the PI and the research subject, the subject's family, or LAR.

The IRB Chair, Vice-Chair(s), or convened IRB may also appoint an unbiased ombudsman to oversee that a subject who is particularly vulnerable receives equitable and ethical treatment throughout the course of the research study. This type of ombudsman should have experience with the vulnerable population at issue or may also be a group of people with an interest in the safety of human research subjects,

generally with a particular research focus. This type of ombudsman is permitted to be an IRB member or affiliated with the Institution.

ii. Third Party Observer to the Informed Consent Process

The IRB Chair, Vice-Chair(s), or convened IRB may appoint an unbiased individual as a third party to observe the informed consent process on behalf of the IRB. The individual may monitor the process of informed consent conducted by the PI with the prospective research subject/LAR.

The third party may collect data on the informed consent process by employing a variety of methods, including but not limited to, a physical presence (monitoring) during the consent process and/or employing written and verbal questionnaires to evaluate the effectiveness of the consent process.

L. Requirement for Re-Consent of Previously Enrolled Subjects

Federal regulations require that information relating to protocol changes, newly identified risks, or other new information that may relate to the subject's willingness to continue to take part in the research must be provided to research participants. Information on significant new findings that present potential of an increase in risks to participants or identify new risks (i.e., revised investigational brochure, protocol, etc.) are to be provided to active research participants immediately and their willingness to continue to participate confirmed. This communication should be well documented. This requirement highlights that the process of informed consent continues throughout the course of the research. Accordingly, during the review of subsequent submissions to an approved protocol (continuation, amendment, adverse event, subject complaint, or deviation) that includes new information, the IRB will make a determination as to whether the reported information requires that previously consented subjects be re-consented with a revised consent form.

Re-consenting may be required for various reasons including, but not limited to, cases where: the study protocol/procedure has been modified; new safety information exists; new alternative treatment becomes available; the original consent form or process was not properly executed (e.g. participants were consented by individuals not listed on the study personnel list or using invalid form); when the potential for the subject's capacity to consent fluctuates; or any other changes as required by the IRB or sponsoring agency/institution.

If re-consenting is required, the investigator is required to prepare and submit a revised consent form that incorporates the new information along with the detailed plan for re-consenting current subjects. In addition, the revised consent form is to be used with all newly enrolled subjects.

M. Subject Withdrawal from a Research Study

A subject may withdrawal from a research study for a variety of reasons or the investigator may decide to end a subject's participation regardless of whether the subject wishes to continue in the study. Investigators are to plan for the possibility of this withdrawal or termination and indicate in consent forms the context in which this may occur for subjects.

Subjects have the right to withdraw from (i.e., discontinue participation in) research at any time (45 CFR 46.116(a)(8)). If a subject decides to withdraw from all components of the study,

the following research activities must end: interacting or intervening with the subject to obtain data for the research, obtaining additional identifiable private information by collecting or receiving this information from any source, and obtaining additional identifiable private information about the subject by observing or recording private behavior.

An investigator may ask a subject who is withdrawing whether the subject wishes to stop specific research activities, such as ending the primary interventional component of a study while continuing to provide follow-up and further data. Under this circumstance, the investigator is to discuss with the subject what study-related interventions, follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, will continue. The investigator must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.

OHRP recommends that for clinical trials, in which the secondary components of the study may be important for the evaluation of safety and effectiveness, the investigator conducting the trial ask to clarify whether the subject wishes to withdrawal from all components or only the intervention. OHRP also recommends that investigators discuss with subjects the importance of collection the follow-up safety data. This is also relevant when an investigator terminates a subject's participation from an intervention; the investigator is to inquire if continued data collection may continue.

The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access, for purposes related to the study, the subject's medical record or other confidential records requiring the subject's consent. However, a researcher may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.