Institutional Review Board Policies and Procedures Manual

SECTION 11: INFORMED CONSENT PROCESS

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 particular 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).

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.

11.2 PARENT CONSENT AND CHILD ASSENT

A. Parental Permission

Before enrolling any minor under the age of 18 into a research study, the investigator is required to obtain parental permission for the child's participation. Specific questions regarding this requirement may be directed to the Director, ORIC, or IRB Chair. In general, the permission of both parents should be obtained before a child is enrolled in research.

The IRB may find it sufficient that one parent or guardian gives permission for a child to participate in a research study when:

- Research risk is not greater than minimal (45 CFR 46.404), or
- Research risk is greater than minimal but there is a prospect of direct benefit to the individual subjects (45 CFR 46.405)

Both parents must give permission for a child to participate in a research study (unless one parent is deceased, unknown, incompetent, or not reasonably available*, or when only one parent/guardian has legal responsibility for the care and custody of the child) when:

- Research risk is greater than minimal with no prospect of direct benefit to individual subjects, but the research is likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406), or

- Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate, a serious problem affecting the health or welfare of children (45 CFR 46.407).

*When only one parent accompanies the child to a visit, they should be asked to provide the phone number and/or address of the other parent. The investigator should contact the other parent to discuss the study and to arrange to obtain consent (phone consent process may be followed). Ideally, this would be done in advance of the visit, as the child may not be enrolled until the absent parent has returned the signed consent form to the investigator (fax, scan/e-mail, or mail). It is important for the investigator to document all attempts to contact the absent parent, along with the basis for any determination that they are "reasonably unavailable."

If the child does not have a parent, the child will have a guardian. The term guardian means "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care" (45 CFR 46.402(e)). In Illinois, this would be an individual appointed by court order with authority to consent to general medical care. Federal law allows a guardian to consent to a child's research participation. However, under Illinois law, a guardian can only consent to a child's participation in research pursuant to a court order. A foster parent is considered a guardian, not a parent. Children who are wards of a county or other agency will have a court-appointed guardian. For such a child to participate in research, a court order must be in place evidencing the following: 1) the guardian's identity and authority to consent to general medical care for the child; and 2) either (i) the guardian's identity and authority to consent to the child's participation in the study, or (ii) the court's approval of the child's participation in the study. If the investigator has questions regarding the process or need for a court order, the investigator should consult with the Department of Legal Affairs. The court order shall be placed in the research record.

i. Parents or Guardians as Research Subjects

At times research that primarily targets children may also include research procedures for the parents of these children. For example, a mother, father, or other guardian of the minor participant may be approached. Consent should be obtained and documented adequately from any individual who is the focus of the research activities. A parental permission signature is not adequate to demonstrate consent by a parent/guardian for their own participation in a research study.

If the parent/guardian participation is limited to data collection (e.g., surveys, questionnaires), the consent may be included as an addendum to the parental permission form. If the parent/guardian participation includes medical chart review, specimen collection, or genetic testing, the Adult Consent templates must be used. Appropriate HIPAA authorization language must be included if PHI will be used.

B. Child Assent

Federal regulations define assent as an "*affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.*" (45 CFR 46.402(b)) This means the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB determines and documents whether obtaining assent is a requirement of all, some, or none of the children in a study. When the IRB determines that assent is not a requirement of

some children, the IRB determines and documents for which children assent is not required. When the IRB determines that assent is not a requirement for some or all children, the IRB determines and documents one or more of the following:

- The children are not capable of providing assent based on the age, maturity, or psychological state.
- The capability of the children is so limited that they cannot reasonably be consulted.
- The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the research.
- Assent can be waived using the criteria for waiver of the consent process.

When the IRB determines that assent is a requirement, the IRB determines whether:

- Assent will be documented.
- The process to document assent.

The IRB has the discretion to judge a child's capacity to assent to the proposed research activity. According to federal regulations, a "child" is a person who has not yet 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.

In order to provide a potential child subject sufficient information to decide whether to assent to research participation, the child should be given an explanation of the proposed research procedures in a language that is appropriate to his or her age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if he or she agrees to participate.

If a child is capable of assent and the IRB requires that assent be sought, it must be obtained before the child can participate in the research activity. Thus, if the child dissents from participating in research, even if his or her parents or guardian has granted permission, the child's decision prevails. However, the IRB may waive the assent requirements if the intervention or procedure involved in the research holds out the prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of research (see below concerning the requirements for waiver of assent). Conversely, if a child assents to participate in research, and parental permission has not been waived by the IRB, the permission of the parents or guardian is also required before the child can be enrolled in the research.

The federal regulations do not specify the order in which parental or guardian permission and child assent should be sought. In general, parental or guardian permission should be sought before seeking the assent of a child, particularly in more than minimal risk research, unless the requirement for obtaining parental or guardian permission can be waived. There might be some cases, however, involving minimal risk research, where it would be reasonable to seek child assent prior to seeking parental permission.

The federal regulations do not require documentation of assent. The IRB has the discretion to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child's age, maturity, and degree of literacy, the IRB decides what form of documentation, if any, is most appropriate. If assent is not waived, the process for obtaining assent, the content of the information provided, and the format of the assent document, if any, depends on the age of the child.

At this Institution, written assent is to be obtained from children 12 to 17 years of age unless explicitly waived by the IRB. All assent documents must be reviewed and approved by the IRB prior to use.

i. Children less than 12 years of age

Written assent is not required for children under the age of 12. Nevertheless, it is appropriate to provide a potential child subject an explanation of the proposed research and obtain verbal assent using language appropriate to his or her age, experience, maturity, and previous experience.

ii. Children aged 12-17

If assent is not waived by the IRB, children in this age group should be fully informed about the research and documented assent should be obtained using the Adolescent Assent Form. If documented assent is not obtained, the reason for not obtaining assent should be noted in the research record for the subject.

iii. Children Who Turn 12 During the Course of the Study

Any child who turns 12 during the course of a study must provide written assent before his or her participation in the study continues, unless a waiver of assent has been obtained from the IRB.

iv. Research Participants Who Turn 18 During the Course of the Study

When a participant who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent (18 years of age) to the procedures involved in ongoing research, the subject's participation in the research is no longer regulated by the requirements of 45 CFR part 46.408 regarding parental or guardian permission and assent.

Unless the IRB determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject.

Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects.

The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(e) of the requirements for obtaining informed consent. A waiver of consent may be considered in those cases in which the now adult subject's continuing participation constitutes no more than minimal risk and meets all requirements for waiver under 45 CFR 46.116(e), including the requirement that the "research could not practicably be carried out without the waiver." For example, subjects enrolled in studies in which all intervention or interaction prescribed by the protocol, including follow-up visits and ongoing data collection, has concluded prior to subjects' reaching adulthood and the only activity that would meet the definition of human subjects research is the maintenance of identifiers for continued data analysis.

C. When Minors Can Consent for Treatment and Research

Federal Regulations at 45 CFR 46.402 define c*hildren* 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. The additional protections in Subpart D, including parental permission, apply to any research in which a subject is a *child*. The definition of who is a child varies by state laws regulating when children may consent for treatment.

In Illinois, the age of majority is 18 years, but there are many situations where minors can consent to treatment (e.g. if the minor is married, emancipated, a parent, or pregnant). Whenever a minor can consent to treatment, the minor is not considered a *child* under the federal regulations and may consent for research for themselves provided they have the capacity to protect their own interests and the research is related to the care for which they have consented. The Guttmacher Institute provides an overview of minor consent laws by state. The Illinois Health and Hospital Association Infographic is another resource that provides guidance on determining when a minor may provide consent in Illinois. The IRB will make the final determination of whether subjects are considered *children* under the federal regulations based on state law.

D. Consent When the Parent of a Child is a Minor as Well

Illinois law does not distinguish between a minor and an adult when defining who is a parent. Statutory provisions of Illinois law allow a minor parent to consent to medical treatment of his or her child.

Research with minors, pregnant minors and their fetuses and children requires special considerations to protect these vulnerable populations and involves complicated ethical issues and regulatory requirements. The decision to allow minors to consent on their own behalf and/or on behalf of their fetuses, neonates, and children will be made by the IRB on a case-by-case basis after careful consideration of the nature of the research, anticipated benefits, and potential risks. After the research is approved by the IRB, it may be subject to further review at the institutional level (such as the Institution's Legal Counsel) before it is initiated.

E. Special Circumstances in Which Minors May Consent

A minor may give informed consent for research when the research includes the following:

- The study provides confidential contraceptives and pregnancy tests to minors if the minor is referred by a physician, a clergyman or a Planned Parenthood agency, or where a serious health hazard would be created by the failure to provide these services.
- Minors aged 12 and over may consent to confidential testing, treatment, and counseling for and vaccination against sexually transmitted infections (STIs).
- Minors aged 12 and older may consent to testing, treatment and counseling for HIV. Minors may also consent to anonymous HIV testing.
- Minors aged 12 and older may consent to confidential outpatient counseling and treatment if they or a family member abuses drugs or alcohol.

The decision to allow minors to consent on their own behalf will be made by the IRB on a case-by-case basis after careful consideration of the nature of the research, anticipated benefits, and potential risks.

F. Special Requirements for Research that involves Children who are Wards (Youth in Care)

Federal regulations at 45 CFR part 46, subpart D provide additional protections for children who are also wards (called "Youth in Care" in Illinois) of the State or any other agency, institution, or entity. These special protections for wards apply to two categories of research:

- Research approved by an IRB under 45 CFR 46.406; or
- Research approved in accordance with the requirements of 45 CFR 46.407 that require a special level of HHS review beyond that provided by the Institutional Review Board (IRB).

As set out in 45 CFR 46.409, before children who are wards of the State or any other agency, institution, or entity can be included in either of the two categories of research referenced above, the research must meet the following conditions:

- The research must be either related to the children's status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards;
- The IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or LAR.

One individual may serve as advocate for more than one child, and must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research. The advocate should represent the individual child subject's interests throughout the child's participation in the research. In addition, the advocate shall not be associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian's organization.

In addition, all research that includes Illinois wards (Youth in Care) and their families require approval by the Illinois Department of Children and Family Services (DCFS) IRB prior to the initiation of the research. Research involving staff, foster parents, grantees and contractors of DCFS may also require this DCFS IRB review. For studies that have already obtained Lurie Children's IRB approval, a stream-lined, expedited process for obtaining subsequent DCFS IRB review is available. More information on how to obtain this approval can be found at: https://www2.illinois.gov/dcfs/aboutus/policy/Pages/com_communications_IRB.aspx

G. Parental Permission Requirements for Research on Dried Blood Spots Obtained Through Newborn Screening

A new provision of the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240) requires federally funded research using newborn dried blood spots collected on or after March 18, 2015 to be considered non-exempt human subjects research. Thus, research that utilizes newborn dried blood spots and of which is federally funded will be required to be reviewed under the HHS protection of human subjects regulations at 45 CFR part 46. Parental permission for the use of the dried blood spots for this federally funded research will be

required and must be obtained prior to use. In addition, continuing research that is federally funded and is conducting research with newborn dried blood spots collected on or after March 18, 2015, will also have to comply with these new requirements. Non-identifiable newborn dried blood spots collected prior to March 18, 2015, may continue to be used in federally funded research without parental permission, and this activity would continue to be considered research that does not involve human subjects under the current human subjects regulations. The NIH recognizes that there is no universal agreement on the optimal timing for collection of parental permission for research purposes. Obtaining permission at the time the dried blood spots are collected may be one option. Ideally, an educational process could take place prior to the process of obtaining permission, and may be provided prenatally or after the birth of the child.

11.3 CONSENTING NON-ENGLISH SPEAKING SUBJECTS

Federal regulations, 45 CFR 46.116 and 117; 21 CFR 50.25 and 50.27, require that informed consent information be presented in a language understandable to the subject, and in most cases that informed consent be documented in writing. Investigators should consider the ethical and legal ramifications of enrolling a subject when there is a language barrier. If subjects do not have a clear understanding of the consent document or are not able to freely ask questions and understand the answers, then their consent will not be truly informed and legally effective. When subjects/families do not speak English, the use of translated consents is always preferred.

A. Translated Consent Forms

If an investigator anticipates that non-English speaking subjects will be enrolled on a study or if the parents or guardians do not speak English, the consent documents should be translated into the native language(s) of potential subjects and/or parents prior to their enrollment. Protocol-specific foreign language consent and assent forms require IRB approval before being used to enroll study subjects. If the investigator does not initially anticipate enrolling non-English speaking subject(s) but later wishes to do so, the consent and assent forms should be submitted as an amendment with the certification of translation.

B. Use of a Translated Consent Form

The informed consent process for enrolling subjects using a translated consent form must meet the following requirements:

i. The investigator must submit the translated document(s) to the IRB for review and approval with a certificate of translation by the translator indicating that the translation is a true representation of the English version.

ii. The PI or person obtaining consent, through the interpreter, must orally present the IRB approved version of the translated consent to the subject, and the subject must be given a written translation of the consent form to read;

iii. Per Institutional policy, every effort should be made to use a professional interpreter. No patient, family, or friend should be utilized as an interpreter. No child under the age of 18 should ever be asked to interpret. If fluent in the language spoken, the principal investigator or another study team member who is authorized to obtain consent, may present the study information directly to the subject/family. Care should be taken to ensure that the interpreter's relationship with the subject does not adversely influence the subject's ability to make an independent decision regarding participation.

iv. The investigator and/or study staff authorized by the IRB to obtain consent must sign the approved translated version of the consent form;

v. The subject/LAR should sign the translated consent form;

C. Use of a Short Form for Informed Consent

Federal regulations 45 CFR 46.117 (and 21 CFR 50.27) include provisions for a consent process that can accommodate an illiterate subject or a subject who cannot read/understand English. For research studies that may encounter subjects in these situations, the regulations allow for the use of a short form in combination with a verbal presentation of information related to the conduct of the research. The occurrence of the verbal informed consent process is documented via a "short form written consent document" (short form).

The short form states that the elements of informed consent have been presented orally to the subject, and that the key information required by 46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The short form does not contain protocol-specific information and should only be used under special circumstances (e.g., the enrollment of illiterate persons or non-English speakers for whom no translated consent form is available) and enrollment of subjects in a study which requires an immediate decision (due to the emergent nature of the research).

The IRB will take into account the complexity of the study and the ability of potential subjects to understand the protocol when presented verbally. The ability to accommodate non-English subjects throughout the course of the research will also be considered to ensure the safety of participants. The IRB must be confident that the research team can readily communicate with participants to assess outcomes and safety.

The use of an interpreter and the "short form" is deemed appropriate for situations where the investigator anticipates that the majority of participants will be fluent in English, however, acknowledges that occasionally non-English speaking patients may be eligible for a research study. ORIC has provided IRB approved translations of a "short form" in several languages (e.g. Spanish, Bosnian, Vietnamese, Polish, Arabic, Russian, etc.) for investigators which can be downloaded from the IRB website.

The informed consent process for enrolling subjects using the short form must meet the following requirements:

i. The PI or person obtaining consent, through the interpreter, must orally present the IRB approved English version of the consent to the subject in a language understandable to the subject, and the subject must be given a written translation of the short form consent document to read;

ii. Per Institutional policy, a professional interpreter should be utilized in the informed consent process. Care should be taken to ensure that the interpreter's relationship with the subject does not adversely influence the subject's ability to make an independent decision regarding participation. Under no circumstances, should an individual under the age of 18 serve as interpreter;

iii. The consent process must be witnessed by an individual who is fluent in both English and the language understandable the subject. The interpreter may serve as the witness;

iv. The IRB shall approve a written summary of what is to be said to the subject or the representative, typically the IRB approved consent English consent form serves as this summary;

v. The investigator and/or study staff authorized by the IRB to obtain consent must sign the approved English version of the consent form;

vi. The subject/LAR should sign the translated short form;

vii. The witness to the consent process must sign both the translated short form and the summary (English informed consent form);

viii. A copy of both the IRB-approved English consent form (i.e., the summary) and the translated version of the short form must be given to the subject/LAR. Copies of both forms must be placed in the subject's study file and medical record (as applicable).

11.4 CONSENTING SUBJECTS WHO LACK DECISIONAL CAPACITY

If an investigator wishes to enroll adults who lack decisional capacity and is unable to provide informed consent themselves, consent must be obtained from a LAR. For the purpose of this policy, "decisional capacity" is defined as "*the ability to understand and appreciate the nature and consequences of a decision regarding medical treatment and the ability to reach and communicate an informed decision in the matter as determined by the attending physician.*" Subjects may lack decisional capacity due to a number of circumstances, such as severe psychiatric disorders, degenerative diseases affecting the brain, impaired consciousness, etc. However, investigators should note that diagnosis of mental illness or mental retardation is not an automatic bar to a determination of decisional capacity; instead, investigators should consider whether individuals with such diagnoses lack decisional capacity using the previously provided definition.

A. Assessing Capacity to Consent

All adults, regardless of condition or diagnosis of disease should be presumed competent to consent unless there is evidence of cognitive impairment or mental disability. Cognitive impairment refers to a psychological disorder, organic impairment, psychiatric disorder, a medical condition, or developmental disorder that diminishes capacity for judgment and reasoning. Subjects dependent on drugs or alcohol, subjects suffering from degenerative diseases, and terminally ill patients may also be compromised in their decision-making ability. Individuals who are incapable of providing consent cannot be enrolled in a study without the consent of a LAR.

Prior to enrollment, an investigator must assess the potential participant's capacity to consent. To do so, the investigator must determine to the best of his or her knowledge whether the subject understands the risks and benefits of the research, the therapeutic options to research, and the voluntary nature of participation. When making this determination, the investigator should ask open-ended questions of the potential subject. The IRB recommends investigators using the following questions as guidelines to assess potential subjects' capacity to consent:

- What will you be asked to do if you participate in this study?
- What are the potential risks of participating in this study?
- What are the potential benefits of participating in this study?
- How long will you be involved in the study?

- Do you know that your participation is voluntary?
- Do you understand that this is research and procedures involved in research are experimental?

The use of open-ended questions is believed to be more effective as it requires that participants vocalize their understanding of the information that has been provided to them.

B. Who May Consent for the Cognitively Impaired

The Illinois Medical Patient Rights Act (410 ILCS 50/) indicates that "no research can be conducted on a patient without prior informed consent of the patient or, if the patient is unable to consent, the patient's guardian, spouse, parent, or authorized agent." The Illinois Health Care Surrogate Act is not applicable to research.

As a general matter, if an adult lacks capacity to consent (e.g., as a result of trauma, mental retardation, some forms of mental illness, or dementia), whether temporary, progressive, or permanent, only a LAR for that adult can give consent for participation in the research, unless the requirement to obtain informed consent is waived by the IRB in accordance with the requirements at 45 CFR 46.116(e)

The LAR is defined as "the individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in research." During the consent process, the LAR should be informed that he/she will have the right to receive information on the research, as well as to withdraw consent for further participation.

If the patient regains decisional capacity during the study, he/she should be told of the LAR's decisions regarding medical treatment and enrollment on the research study. The research participant should be given information about the research and told that he/she is free to withdraw from the study if so desired. If the study subject (patient) wishes to remain on the study, he/she should sign the consent form to document this decision.

If an investigator anticipates that he/she may enroll patients who lack decisional capacity, the investigator should clarify this point in the IRB application and the protocol (when possible). In the IRB application, the PI will be asked to describe the cognitive impairment of the potential subjects, how it will be assessed, and by whom. The PI will also be asked to describe the plan for obtaining consent from the patient when he/she is capable if the cognitive impairment is temporary.

Because of the *possibility* that once a patient is capable of consenting to participate in the study but refuses to participate, the PI is required to describe the plans for what will be done with the data and specimens collected prior to the participant's dissent.

11.5 WAIVERS OF INFORMED CONSENT, PARENTAL PERMISSION, AND ASSENT

A. Waivers of Consent Requirements

At 45 CFR 46.116(e) the regulations identify when IRBs may waive or approve an alteration of informed consent/assent. The investigator may request this waiver in the research plan for research that meets four specified criteria:

i. The research involves no more than minimal risk to the subjects (this includes the minimal risk studies as defined in 21 CFR 50.3(k) or 56.102(i))

ii. The research could not practicably be carried out without the requested waiver or alteration;

iii. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

iv. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

v. Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

If an investigator feels that his or her research qualifies for an alteration of the required elements of informed consent or a waiver of the requirement to obtain informed consent, he or she must indicate this as part of the IRB application. An investigator must provide a protocol-specific justification that documents how the research meets all of the above-referenced criteria. The IRB will evaluate the investigator's explanation against the relevant federal regulations and will decide to support or deny the investigator's request for a waiver or alteration. When considering the issue of "practicability," the IRB must arrive at the determination that a requirement for informed consent would mean that the research would not be practicably carried out without the waiver.

B. Waiver of the Requirement for Documented (Signed) Informed Consent

Federal regulations generally require not only that informed consent be obtained from subjects of research, but also, that consent be documented via a signature on a study consent form.

However, federal regulations include a provision that allows the IRB to approve an informed consent process that does not require "documentation." In such instances, the IRB may determine that subjects' informed consent can be obtained without collecting signatures on a written consent document. The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects in research if it finds that:

i. For non-FDA regulated research, the only record linking the subject and the research would be the consent document, and the principal risk of study participation would be potential harm resulting from a breach of confidentiality. In such a case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

ii. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

iii. If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

When the requirement for the investigator to obtain a signed consent form is waived by the IRB under category ii above, ORIC routinely requires that the investigator provide subjects with written information about the research – usually, an information sheet containing the basic elements of informed consent. If the waiver is obtained under category (i) above, an informed

consent document is required to be prepared by the investigator, as each subject must be presented with the decision to sign the consent form.

When a waiver is granted, investigators are still responsible for fulfilling all of the basic principles of informed consent (above). Investigators who receive this waiver are still required to conduct a comprehensive oral consent process to obtain voluntary participation of subjects.

C. Waivers of Informed Consent when working with a state or local public benefit or service program

To obtain a waiver or alteration of informed consent under this provision, the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and the research could not practicably be carried out without the waiver or alteration.

Note that only public benefit or service program research activities that are under state or local authority meet this criterion; similar research conducted under federal authority would not qualify here and is treated elsewhere in the regulations. Research conducted by or subject to the approval of only a private entity also would not qualify for this exception to the informed consent requirement.

D. Waiver of Parental Permission

In accordance with the federal regulations (45 CFR 46.408(c)), the IRB may waive the requirement for parental permission if it determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism is in place to protect the children, provided that the research is not FDA-regulated, and provided that the waiver is not inconsistent with federal, state, or local law, or other Institutional policy. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

If an investigator feels that his or her research qualifies for a waiver of parental permission, he or she must indicate this as part of the IRB application. An investigator must provide a protocol-specific justification that documents how the research meets the above-referenced criteria. The IRB will evaluate the investigator's explanation against the relevant federal regulations and will decide to support or deny the investigator's request for a waiver.

E. Waiver of Child Assent

In accordance with the federal regulations, the IRB may waive the requirement for assent under the following two circumstances (45 CFR 46.408(a) and 21 CFR 50.55(c)):

- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- The interventions or procedures involved in the research hold out a prospect of direct benefit that is important to the health or well-being of the children and is available *only* in the context of the research.

Waivers of assent must be obtained prior to conducting any protocol-related procedures. If a waiver of assent is subsequently needed after initial IRB approval for an individual subject, the IRB Chair, Vice Chair or designee may grant a waiver if the above criteria are met. The request for the waiver is to be emailed to the IRB with the following documentation: study title, IRB number, and name of PI; the reason the child is not capable of assenting (e.g., cognitive delay due to disease); and confirmation that parental permission will be/has been obtained. An email documenting the waiver of assent will be returned to the PI and saved in the study file in Cayuse IRB. If the cognitive capability of the child to assent is temporary, and changes during study participation in such that he/she is able to provide assent (verbal or written) later, assent from the child should be obtained at that time.

F. Waiver or Alteration of Written HIPAA Authorization

The Privacy Rule contains criteria for waiver or alterations of HIPAA Authorizations by an IRB or another review body called a Privacy Board. The IRB serves as the Institution's Privacy Board for Research. The IRB may waive or approve and alteration of HIPAA Authorization provided that the research meets the criteria outlined in 45 CFR 164.512(i)(2)(ii):

i. The use or disclosure of protected health information (PHI) involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

    1. an adequate plan to protect the identifiers from improper use and disclosure;
    2. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
    3. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

ii. The research could not practicably be conducted without the waiver or alteration; and

iii. The research could not practicably be conducted without access to and use of the protected health information.

The IRB may also issue a *partial* waiver of HIPAA Authorization (45 CFR164.512(i)(1)(i)). A partial waiver of the Authorization requirements may be requested, for instance, to allow a researcher to obtain PHI as necessary to recruit individuals into a study.

A waiver or alteration of written HIPAA Authorization may not apply if the investigator is releasing any of the following sensitive identifiable information outside the covered entity:

- HIV/AIDS related health information and/or records (a participant 12 or over must authorize this release)

- Behavioral or mental health information and/or records (release must be witnessed and the participant 12 or over must authorize this release)
- Information about sexually transmitted disease (a participant 12 or over must authorize this release)
- Pregnancy (a participant 12 or over must authorize this release)
- Birth control (a participant 12 or over must authorize this release)
- Drug/alcohol diagnosis, treatment, and/or referral information (a participant 12 or over must authorize this release)
- Genetic testing information and/or records
- Information about sexual assault/abuse
- Information about child abuse and neglect
- Domestic abuse of an adult with a disability

For more information, refer to the Administrative Policy and Procedure Manual "Release of Information" (only accessible via The Portal).

G. Waiver of Informed Consent for Planned Research Conducted in Emergency Settings

There are some types of prospective research that involve emergency medical interventions in which informed consent cannot be obtained. Under 21 CFR 40.24, the IRB may approve an exception to the informed consent requirement for human subjects research if the study involves the use of an intervention (drug, biologic or device regulated by the FDA) to treat a life-threatening condition for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent. The IRB must find and document that the study meets the following requirements:

- The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining informed consent is not feasible because:
    - The subjects will not be able to give their informed consent as a result of their medical condition;
    - The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
    - There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- Participation in the research holds out the prospect of direct benefit to the subjects because:
    - Subjects are facing a life-threatening situation that necessitates intervention;

- Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
- Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

- The clinical investigation could not practicably be carried out without the waiver.
- The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.
- The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- There are informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.
- Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
  - Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  - Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
  - Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
  - If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family

members and make this information available to the IRB at the time of continuing review.

This clinical investigation must be carried out under a separate IND or IDE, and the application to the FDA must clearly identify that the protocol includes subjects who are unable to consent.

If the IRB determines that the investigation cannot be approved due to the above criteria not being met or due to an ethical concern with the study, the decision will be documented and returned in writing to the investigator.

For research not subject to the FDA regulations, the Secretary of DHHS issued a notice in the Federal Register that waived the general requirements for waiver under §46.101(i). Consistent with this waiver, the IRB may waive the requirement for informed consent for planned emergency research provided the IRB reviews and approves both the activity and a waiver of informed consent and must:

(i) find and document that the research is not subject to 21 CFR 50 regulations, and

(ii) find, document, and report to the OHRP that the conditions listed above have been met relative to the research.

Because of special regulatory limitations relating to research involving fetuses, pregnant women, and human in vitro fertilization, and research involving prisoners, this waiver is inapplicable to these categories of research.

11.6 CONSENT FOR SURVEYS

Research studies where the involvement of subjects is limited to completing a survey may meet the criteria for exemption under category 2 - research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior. A research study that is limited to surveys does not meet the criteria for exemption under category 2 if the following are applicable:

i. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; ***and***

ii. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption criteria 2 would not apply to surveys that are: 1) conducted with minors (younger than 18), 2) prisoners, and/or 4) more than minimal risk. A survey research study that meets the exemption criteria should be submitted to the IRB via Cayuse IRB and must include a copy of the survey, the information sheet (see below), and the copy of the letter or email that will be used to recruit participants to complete the survey.

Survey research that does not meet the criteria for exemption under category 2 should be submitted to the IRB as an initial submission for consideration for expedited or full board review.

Research studies that involve only surveys may meet the requirements for waiver of documentation of informed consent (per 45 CFR 46.117(c).

When a research study proposes to collect information without obtaining documentation of consent, a statement that contains the following is required to be included with the survey as an information sheet:

- The investigator's name and the study title
- A statement that completing the survey is voluntary and that any question may be skipped
- An short explanation of the purpose of the study
- How long the survey will take to complete
- If the survey will ask for any identifiers (e.g. name, email address, etc.) or if it will be anonymous
- If required, a statement that indicates subjects must be 18 to complete the survey
- Any anonymous information from the survey, once entered into the study database, cannot be removed
- A statement that describes the risks and benefits
- A statement that describes any compensation for taking the survey
- A statement which tells the participant that by filling out the survey consent is implied
- In the case that the survey will be conducted online, the statement must also indicate that information can only be kept as secure as any other online communication
- Investigator's (or other study team member's) contact information for questions about the study

If no consent documentation is to be obtained, a request for waiver of informed consent/assent documentation must be included in the initial submission. The above information must be presented to the research subjects prior to the start and completion of the survey.

i. Surveys Collecting PHI and Sensitive Information

Sensitive information is defined as information that would cause the respondent to hesitate before providing an answer or not respond at all. Some respondents may stop taking the survey all together because a sensitive question turns them off from the process. Sensitive questions include questions regarding substance abuse, personal experiences of sexual or physical abuse, attitudes towards race, ethnicity, or religion, family planning, mental health history, economic status that includes reporting of income, criminal history, and other possible material.

When a research study proposes to collect individual identifiers (i.e. one or more of the 18 PHI identifiers defined by HIPAA) and sensitive information, all study participants must be consented with an IRB approved informed consent document. When a research study proposes to survey minors and includes sensitive information, whether it is identifiable or not, written parent/guardian/LAR permission and assent must be obtained. In the informed consent document, the following information must be included in addition to the already required elements:

a. A statement that completing the survey is voluntary and that any question may be skipped

b. An explanation which describes how the survey will be linked to the potential identifying or sensitive information

c. A description of how and if their data may be removed from the study database upon completion

In the case where the survey is to be conducted through a website, the IRB requires the PI to obtain a post-approval/pre-implementation review of the internet security arrangements by the Director of Information Technology related to the internet sites in which PHI or sensitive health information is being requested of or entered by or on behalf of the study participants. More information regarding the requirements for internet research can be found in that section of the IRB Policy and Procedure Manual.

11.7 ALTERNATE METHODS OF CONSENT

For some research studies, consenting participants may require a differing set of methods to including obtaining consent in person or remotely. When alternate methods of obtaining consent are required, the IRB must approve the consent process, the mechanisms of obtaining consent and documentation of the consent discussion.

A. Consenting Participants over the Phone

In order for an investigator to obtain consent or assent over the phone, a full consent and assent form (if applicable) approved by the IRB must be provided to the potential participant/parent/LAR in advance (i.e., via e-mail, fax or mail) to review before and during the consent process.

An information sheet/cover letter may also be included in the documents sent to the subject/parent/LAR during the consent process. An information sheet/cover letter is required if the first introduction to the research study will only be via mail/email or phone call (see also Section 10 regarding subject recruitment).

An information sheet/cover letter should include the following:

- The PI's name and the study title
- The purpose of the study
- How the subject was identified for the study
- That participation is voluntary and that the subject has a right to withdrawal at any time (include specifics about what data may be withdrawn if a subject wishes to discontinue participation)
- A description of when a member from the study team will contact them to discuss the study
- That no documents should be signed prior to talking to a member of the study team

A member from the study team will then need to call the subject/parent/LAR to explain the study in detail and review the informed consent documents with the subject or parent/LAR. If the subject or parent/LAR consents to participate, they will sign his/her copies of the informed

consent documents. The study team member obtaining consent will sign a copy at the same time. If needed, the child assent can be obtained over the phone in the same way the parental permission was obtained. The phone consent process must then be documented in the study file.

The subject or parent/LAR will then be required to send back their signed copies of the informed consent documents to the study team and the two signature pages are to be combined. The documents can be sent either by mail, fax, or scanned and emailed. The subject or parent/LAR need not provide the investigator with the original signed consent documents. The subject or parent/LAR must be provided a copy of the fully executed, signed informed consent documents. Once this has been completed, any study procedures (e.g., survey, screening visit, etc.) may be sent to the subjects or parents or scheduled by the study team.

B. Obtaining Electronic Consent

OHRP allows electronic signature of consent documents as long as the IRB has considered applicable issues such as how the electronic signature is being created, if the signature can be shown to be legitimate, and if the consent or permission document can be produced in hard copy for review by the potential subject. OHRP does not mandate a specific method of obtaining electronic informed consent (e-consent).

Informed consent may be obtained utilizing an electronic platform in which an IRB approved consent document is presented for the subject/LAR to sign electronically. Prior to obtaining e-consent, the consent form, process and platform of choice must be submitted to the IRB for review and approval. The submission must include the platform to be utilized what information will be accessed, stored, and used by any third party, and their terms and conditions, if applicable.

In addition, the FDA states that the IRB "review any optional questions or methods used to gauge subject comprehension of key study elements. The IRB should also review the usability of the e-consent materials to ensure that they are easy to navigate. If the program uses hyperlinks to convey study-related information, IRBs should review the contents to which subjects are referred in order to determine if the study-related information that has been supplied is accurate and appropriate."

When a subject electronically signs an e-consent form, there must be confidence that the signature can be attributed to the actual person signing the form, and that the person cannot repudiate the signature once invoked. Therefore, prior to utilizing the e-consent platform, understand and document the verification steps to assure the authenticity of the signature and it is not possible to delete the signature. Federal regulations describe variety of methods to obtain a valid electronic signatures such as using computer readable ID-cards, biometrics, digital signatures and user name and password combinations; however, other methods may be utilized.

Obtaining e-consent follows the same principles as in-person informed consent: the e-consent document is to contain all elements of consent, the consent process must allow for time for questions, and signatures given voluntarily. The consent process is to be documented, a copy is to be provided to subjects/LAR, and the consent must be retained securely and inspection ready. If HIPAA Authorization is also obtained with an electronic signature, the signed form must be returned to the subject/LAR.

For FDA regulated studies (i.e. the investigation of a drug, device, or biologic) the platform for the e-consent will require compliance with 21 CFR Part 11. Documentation of the platform's compliance must be included in the IRB submission for review and confirmation.

i. Obtaining consent with an electronic signature

When a potential subject has been identified for the study, the IRB approved informed consent documents are to be made available via display within the electronic platform. The person obtaining consent is to present the consent information in person, or this may be accomplished remotely via a call or with an IRB approved application for face-to-face or verbal communication with the subject or parent/LAR.

If the subject or parent/LAR consents to participate, they will provide their signature on the electronic version of the consent. The study team member obtaining consent is to sign a copy at the same time. If needed, the child assent can be obtained in the same way the parental permission was obtained. The e-consent process must then be documented in the study file.

The subject or parent/LAR must be provided a copy of the fully executed, signed informed consent/assent form either in hard copy or as an electronic file that can be stored on his or her own personal device of choice. Once this has been completed, any study procedures (e.g., survey, screening visit, etc.) may be sent to the subjects or parents or scheduled by the study team.

ii. Waiver of Documentation of e-Consent

The method of utilizing a "Click to Agree" mechanism is not to be considered an electronic signature. An appropriate waiver of documentation of consent must be obtained for this e-consent mechanism.

When the IRB approves a waiver of documentation of e-consent, the subject or parent/LAR must be presented with an information sheet prior to giving consent/permission. The information sheet is to be reviewed and approved by the IRB and the IRB template utilized. This information sheet must be presented in the electronic platform prior to obtaining consent to participate.

Similar to "paper" in-person consent documentation waiver, a consent process to present the information to the subject/LAR must still occur. It is recommend to also include an option for the subject/LAR retain a copy of the information sheet.