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.