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IRB REFERENCE MANUAL
SECTION 16
INFORMED CONSENT

16.0 INFORMED CONSENT

16.1 Informed Consent for Human Subject Research

16.1.1 Ethical Foundation

Informed consent is one of the primary ethical considerations in research involving human participants. **The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research** describes the purpose of consent as the mechanism to ensure that participants understand the research study and voluntarily agree to participate.

The Principal Investigator (PI) and study team members should consider that *consent is a process;* not simply a form that potential study participants must sign. The process of informed consent does not end at the time of obtaining initial informed consent, rather than a one-time event, it is a dynamic and ongoing process throughout a subject's participation in the research study.

16.1.2 Regulatory Requirements for Informed Consent

Federal requirements mandate the type of consent that may be obtained, the elements that should be present in a consent explanation, and who may obtain and give consent for research purposes. Federal requirements for informed consent must meet the regulatory requirements of the U.S. Department of Health and Human Services (HHS) 45 CFR 46.116 and the US Food and Drug Administration (FDA) 21 CFR 50.20. Under these regulations there are six general requirements for informed consent:

a. **Consent Required**
Investigators may involve human participants in research only with the consent of the participant or the participants' legally authorized representative (LAR), unless the requirement for consent is waived. There are exceptions for waiver of consent, but waivers are highly regulated and must be justified.

b. **Voluntary Participation**
The potential study participant must be given enough time to consider whether or not to participate in the research, and the possibility of coercion or undue influence should be minimized.

c. **Understandable Language**
Consent explanations must be in language understandable to the potential study participant or the individual's legally authorized representative.

d. **Waiver of Rights Prohibited**
The consent may not include language through which the participant or their representative is made to waive the participant's legal rights or releases the investigator, the sponsor, the institution or its agents from liability for negligence.

e. **Key Information**
Informed consent must 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. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

f. **Organized to Assist Understanding**
Informed consent must 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.

NOTE: While 45 CFR 46.116(a) permits a broad consent (which may be obtained with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens), The Christ Hospital (TCH) Institutional Review Board (IRB) will not approve a broad consent process.

16.2 The Informed Consent Process

Under the federal regulations, investigators must obtain "legally effective" informed consent in order to enroll a person into a research study. The Principal Investigator is responsible for devising a process for obtaining informed consent that outlines how the investigator plans to communicate the details about the research study to potential subjects. It should include a detailed description of from

whom informed consent may be obtained, including who will obtain informed consent and when, where and how the consent process will take place.

16.2.1 Legal Efficacy

Informed consent is legally effective if the consent is:

a. Obtained from the subject or the subject's legally authorized representative, and
b. Documented in a manner that is consistent with the federal HHS and FDA regulations on protection of human subjects and with the applicable laws of the jurisdiction in which the research is conducted, and
c. Obtained under circumstances that:
    1) Provide the prospective subject or the legally authorized representative sufficient opportunity to consider whether to participate in the research,
    2) Minimize the possibility of coercion or undue influence, and
    3) Respect the privacy of the potential participant by taking place in a setting that is not open to the public.

The information provided should be in language that is understandable to the subject or the legally authorized representative. No informed consent may include any exculpatory language (language that waives or appears to waive any of the participant's legal rights or releases, or appears to release, the investigator, the sponsor, the institution or its agents from liability for negligence).

16.2.2 Mechanisms for Obtaining Informed Consent

Federal regulations provide two possible mechanisms for obtaining informed consent from a research participant:

a. A process with consent documented by having the appropriate person sign a written IRB-approved consent document, or
b. A process involving a waiver of documentation of consent that has been approved by the IRB

16.2.3 Documentation of the Informed Consent Process

Generally, the IRB requires consent to be documented (ref. 45 CFR 46.117; 21 CFR 50.27) by a written consent form that includes all the required elements and all appropriate optional elements approved by the IRB prior to use. An IRB-approved consent document will contain the date of IRB approval. Unless the requirement for consent is waived by the IRB, the written consent form must be reviewed with the potential research participant (or the participant's legally authorized representative) and signed and dated by the participant or the participant's representative.

Such actions must occur before any research procedures (including screening) or research data collection can begin. The consent form should also be signed and dated by the individual who obtains the participant's consent.

16.2.4 Waiver or Alteration of Informed Consent

Per federal regulations 45 CFR 46.116, a waiver of one or more elements of consent is permitted provided that the research presents no more than minimal risk and meets specific criteria. Alteration of consent is appropriate if one or more of the required elements is not relevant to the research activity. Complete waiver of consent is also permitted and most frequently granted for retrospective research, but also possible for some types of prospective research. The investigator seeking permission for an alteration or waiver of consent should include the request for alteration or waiver in the study application.

a. **Non-FDA Regulated Research**

For non-FDA-regulated research, the IRB may waive or alter informed consent requirements only if it finds and documents that the criteria listed in 45 CFR 46.116(f) are satisfied as well as any other applicable regulations of sponsoring federal agencies and state and local laws and regulations. The IRB may approve a request for an alteration or waiver of informed consent for a non-FDA regulated study if the study meets the following criteria:

1) The research involves no more than minimal risk to the participants
2) The research could not practicably be carried out without the waiver or alteration
3) 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
4) The alteration or waiver will not adversely affect the rights and welfare of the participants, and
5) Whenever appropriate, the participants will be provided with additional pertinent information after participation

Public Demonstration Projects

A waiver or alteration of the consent process may be requested for a public demonstration project conducted or approved by state or local government officials. The following criteria apply:

1) The research is conducted by or approved by state or local government officials

2) The research or demonstration project 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 change in or alternatives to those programs or procedures
    iv. Possible changes in methods or levels of payment for benefits or services under those programs
3) The research cannot practicably be carried out without the waiver or alteration
4) The research is not regulated by the FDA

b. **Research Subject to FDA Requirements**
The FDA has provided guidance on regulations governing informed consent for studies that involve no more than minimal risk to human subjects for which obtaining informed consent is not practicable. For investigations under the jurisdiction of the FDA, the IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent as set forth in 21 CFR 50.25, or waives the requirements to obtain informed consent when the IRB finds and documents that such approval is supported by requirements noted in 16.2.4(a) above. (Ref. FDA Guidance: IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects, III. Discussion, page 3)

16.2.5 Waiver of Documentation of Informed Consent

A waiver of documentation of consent must meet the regulatory requirements of HHS 45 CFR 46.117 and FDA 21 CFR 56.109. This may include an oral consent process or an electronic consent process by which a legally effective signature will not be obtained. The investigator should submit this request for waiver of documentation of consent with the study application and must include a script that the consent designee will use with potential study participants or which will be made available electronically. The script must include all the required consent elements and, when private health information is to be collected, the elements required for HIPAA privacy authorization. Details about the consent (e.g., date, time, identity of consent designee) should be recorded in the study record by the consent designee. If the project involves clinical care, details about the consent should also be added to the clinical record. Note that since the HIPAA authorization provided in an oral or electronic consent process would not be in writing, investigators should request that the IRB grant an alteration to the HIPAA written signature requirement in the application submitted in Mentor IRB.

a. **Non-FDA Regulated Research**
The IRB may approve a request for a waiver of documentation of consent for non-FDA regulated studies under three circumstances:

1) The only record linking participants to the research would be the consent document and, the principal risk to the participant would be potential harm resulting from a breach of confidentiality. In this case, each participant will be asked if he/she wants documentation linking him/her to the research and the participant's wishes will govern; or
2) The research presents no more than minimal risk to the participants and involves no procedures for which written consent is normally required outside of the research context; or,
3) 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.

Waiver of Documentation of the Consent Process: Screening, Recruiting, and Determining Eligibility
An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if the following conditions are met:

1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens, and

Ref. 45 CFR46.116(g)(1) and (2)

b. **Research Subject to FDA Requirements**
For FDA-regulated studies, waiver of documentation is only permitted if the study presents no more than minimal risk. The IRB shall require documentation of informed consent in accordance with 21 CFR 50.27 except as follows:

1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; - or -
2) The IRB may, for some or all subjects, find that the requirements in 21 CFR 50.24 for an exception from informed consent for emergency research are met. Ref. 21 CFR 56.109(c); SOP 1.10 Emergency Use Exemption

Waiver of Documentation of the Consent Process – Consent Normally Not Required

In cases where documentation is waived where consent is normally not required outside the research context, the IRB shall require that:

1) The oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure.
2) The IRB determines whether the investigator should provide subjects with a written statement regarding the research (21 CFR 56.109(d)). Such a document requires IRB approval.

16.3 Describing the Informed Consent Process

16.3.1 Who May Obtain Informed Consent?

The Principal Investigator of an IRB-approved research study is ultimately responsible for the conduct of the study. Both the consent process and the consent form must be approved by the IRB. The Principal Investigator must ensure that informed consent from each potential research participant is:

a. Obtained by an IRB-approved consent designee, and
b. Documented (if required) using the method approved by the IRB. Unless the IRB has approved a waiver of the requirement to obtain consent, informed consent must be obtained before the participant takes part in any aspect of the research study.

The investigators or other key research personnel listed in the IRB application may obtain consent only after the IRB grants approval of each key research personnel. As part of the application process, each individual who interacts with potential research participants in order to obtain consent must complete Human Subjects Research (HSR) training through CITI. The Principal Investigator must also confirm that individuals who will be obtaining consent from research participants have been trained by the PI. Each of the consenters must be knowledgeable

about the study and capable of answering study-related questions posed by the potential research study participant. Additionally, consenters must not have a conflict of interest, financial or otherwise, associated with the research. Investigators and other key research personnel with conflicts of interest must report those conflicts to the IRB.

16.3.2 When May Informed Consent be Obtained?

The informed consent process description must include details about the timing of informed consent. Potential participants should have adequate time to review the consent form, ask questions about the research, and consult with family, friends, or others (if desired) before signing the consent depending on the type of study and the risk(s) associated with it. For example, in research involving elective procedures or scheduled therapy, potential participants should be given ample time to consider participation and should not be solicited immediately before beginning the procedure. However, in certain types of research involving emergent procedures this may not be feasible.

16.3.3 Where May Informed Consent be Obtained?

In-person communication between investigators and study candidates is always the preferred scenario, with ample time to discuss issues and answer questions. At times, however, this may not be necessary nor feasible, e.g., when conducting a straightforward minimal risk survey study which may be readily explained in a consent without the need for much education or interaction. However, consenting for a greater than minimal risk interventional study, even if done remotely, must allow for education, questioning and dialogue.

Methods other than an "in person" consent discussion may be acceptable if those methods (1) allow for an adequate exchange of information, (2) ensure that the signee of the consent form is the person who plans to enroll as a subject or is the legally authorized representative (LAR) of the subject, and (3) unless waived, document consent including the signature and date obtained from the subject or LAR.

No single set of recommendations fit all research needs. Options vary with the risk level and applicable regulations. Investigators should consider what would be feasible or preferable for the subject population and propose multiple or contingency plans to meet situational or individual participant needs.

a. **Remote Consent Process**

The *remote consent* process must be prospectively reviewed and approved by the IRB. The proposed process should be outlined in the Mentor application (Informed Consent Process sub-section) and should include how (1) the consent form will be

presented/reviewed, (2) signatures will be obtained, (3) copies will be provided to subjects. If applicable, screenshots showing the final formatting and features that the subjects would see should be provided. The remote consent process may vary depending upon the risk level. The intent is to receive a signed and dated document for research unless a waiver of consent or a waiver of documentation of consent has been approved by the IRB.

Note: The process for each individual research type should be followed as outlined below:

1) **Remote Process for Minimal Risk Research <u>with</u> a Waiver of Documentation of Consent**
   Research conducted using a Waiver of Documentation of Informed Consent requires a consent form (e.g., cover letter, verbal script) and an outline of the informed consent process. However, the investigator does not have to collect a signed document.

   i. If consent is not built into the data collection instrument, mail, fax, or email the consent form to the subject in advance.
   ii. After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent, answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary.
   iii. Document the conversation by noting the date, names of individuals present, how the process was conducted, discussion points, and whether the person agreed to enroll.

2) **Remote Process for Minimal Risk Research *or* Greater Than Minimal Risk Research <u>Not Subject</u> to FDA Regulation**
   Written informed consent must be documented using a written informed consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

   i. Mail, fax or email the consent form and HIPAA Authorization (if applicable) to the potential subject and/or LAR in advance of the remote

discussion between the consent designee and the participant. The PI must obtain advance IRB approval if a LAR is involved.

ii. After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent, answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary.

iii. Document the conversation by noting the date, name(s) of individual(s) present, how the process was conducted, discussion points, and how the signed document is to be returned.

iv. The The subject then returns the signed and dated document via a prepaid envelope, OR by scanning or photographing the signed and dated document and then sending the scan/photo to the investigator by email/fax/upload.

v. When the investigator receives the signed and dated consent form, the person who conducted the consent conference signs his/her name and enters the current date on the form.

vi. Study procedures should not be initiated until the subject's signed consent document is received.

vii. Ensure that the subject is provided with a copy of the form(s) he/she signed.

viii. If added security is needed or if HIPAA applies to the research, employ cybersecurity precautions or secure/HIPAA video conferencing as applicable. Refer to Question 10 on HHS guidance FAQ's on Telehealth during COVID-19 during COVID-19 regarding "non-public facing" platforms that ensure only the intended parties participate in the video conferencing. Unacceptable public-facing products are also listed.

3) **Process for Greater Than Minimal Risk Research Subject to FDA Regulation**

Written informed consent must be documented using a written informed consent form approved by the IRB and signed and dated (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

i. Mail fax or email the consent form and HIPAA Authorization (if applicable) to the potential subject and/or LAR in advance of the remote discussion between the consent designee and the participant. The PI must obtain advance IRB approval if a LAR is involved.
ii. After the potential subject/LAR has received the form, verify him/her/them as the correct individual(s) through phone or video, talk through the consent, answer questions, and ensure that the subject/LAR understands the consent and that consent is voluntary
iii. Document the conversation by noting the date, name(s) of individual(s) present, how the process was conducted, discussion points, and how the signed consent form is to be returned.
iv. The subject then returns the signed and dated consent form via a prepaid envelope, OR by scanning or photographing the signed and dated consent form and then sending the scan/photo to the investigator by email/fax/upload.
v. When the investigator receives the signed and dated consent form, the person who conducted the consent conference signs his/her name and enters the current date on the form.
vi. Study procedures should not be initiated until the subject's signed consent form is received.
vii. Ensure that the subject is provided with a copy of the form(s) he/she signed.
viii. If added security is needed or if HIPAA applies to the research, employ cybersecurity precautions or secure/HIPAA video conferencing as applicable. Refer to Question 10 on HHS guidance FAQ's on Telehealth during COVID-19 during COVID-19 regarding "non-public facing" platforms that ensure only the intended parties participate in the video conferencing. Unacceptable public-facing products are also listed.

b. **Electronic Informed Consent**

Electronic consent (e-consent) refers to the use of electronic systems and processes that may employ multiple types of electronic media including text, graphics, audio, video, podcasts,

passive and interactive websites, biological recognition devices, and card readers to convey information related to the study and to obtain and document informed consent.

The e-consent process should have the capability to

1) Prove that the actual signer is the intended signer,
2) Allow the signer to deny the signature, and
3) Contain an assurance that neither the record nor the signature has been altered from the moment of signing; to achieve this, signatures executed to electronc records shall be linked to their respective electronic records to ensure that the document cannot be modified or otherwise tampered with. Ref 21 CFR 11.70

If using a PDF format to collect a signature, set verification preferences in advance. This helps ensure that Digital Signatures are valid when a PDF is opened and verification details appear with the signature. Refer to Adobe Validating Digital Signatures.

c. **Eletronic Consent and FDA Regulated Research**

The process of e-consenting differs depending on regulation. FDA regulated research requires that software systems be compliant with all requirements under FDA Part 11 regulation (e.g., restricted access, administrative controls, training, identity verification, etc.). Ref. FDA guidance Part 11, Electronic Records; Electronic Signatures – Scope and Application; 21 CFR Part 11

The FDA does not certify systems for Part 11 compliance. Sponsors may provide Part 11 compliant electronic consent. For investigator-initiated research, refer to Part 11 options such as DocuSign Part 11 or Adobe Sign Part 11.

Generally, there is no "out of the box" software solution as the customer is responsible for setting features, demonstrating compliance, providing/documenting training, and administering operational policies and procedures. It is the investigator's responsibility to be able to demonstrate that the software is fit for its intended use and the system meets applicable regulations should your protocol be audited. A statement may be requested from the sponsor or vendor of the electronic system used for obtaining the electronic signature verifying that the system meets requirements contained in Part 11 and maintains documentation that your site has fulfilled applicable customer requirements such as training, password controls, etc.

d. **Capturing Consent on Electronic Systems**
To capture consent on electronic systems, one may use:

1) **Electronic Signatures**
A computer data compilation of any symbol(s) executed, adopted, or authorized by an individual to be a legally binding equivalent of the individual's handwritten signature. Methods include computer readable ID cards, biometrics, digital (cryptographic) signatures, and user/password combinations. Electronic signatures must comply with 21 CFR Parts 11.50 and *11.70* requirements including:
   i. The printed name of the signer;
   ii. The date and time when the signature was executed;
   iii. The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

2) **Handwritten Signatures Executed to Electronic Records**
Hand-scripted signatures executed to electronic records may be:

   i. Obtained by signing with a stylus, finger, or cursor drawing;
   ii. Used in a hybrid process where the only electronic component is the documentation (signature) of informed consent.

Handwritten signatures executed to electronic records must comply with 21 CFR 11.7 and should be linked to their respective electronic records to ensure that it cannot be excised, copied, or otherwise transferred (i.e., tampered with).

e. **Additional Considerations for Subjects in Medical Isolation**
FDA Covid-19 Guidance provides the process which would be considered to satisfy FDA's informed consent documentation requirement when electronic informed consent is not available nor feasible:

1) An unsigned consent form, and HIPAA Authorization, if applicable, is provided to the patient or LAR by a healthcare worker who can enter the room.

2) If in-person communication with the patient in isolation is not feasible or safe, the investigator arranges a three-way call or video conference with the patient, an impartial witness, and, if desired and feasible, additional people as requested by the patient. To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
    i. Identification of who is on the call
    ii. Review of the informed consent document with the patient by the investigator/designee and response to any questions the patient may have
    iii. Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document which is in their possession
3) If the signed and dated paper consent document <u>can</u> be safely collected, the person who conducted the consent conference prints his/her/their name on the form, signs the form and enters the current date, then provides the subject with a copy of the form he/she/they signed.
4) If the signed informed consent document <u>cannot</u> be safely collected from the patient's location and included in the study records, the FDA considers the following two options acceptable for providing documentation that the patient signed the informed consent document:
    i. **Method 1: A photograph of the signed and dated document may be transmitted to the investigator or research staff.** The patient (or an individual in the room) takes a photograph of the signed informed consent document and sends it to the investigator/designee. A trial team member enters the photograph into the trial records along with an attestation that states how the photograph was obtained and that it is a photograph of the informed consent document signed by the patient.
    ii. **Method 2: A witness can attest to the signature, but a photograph of the signed informed consent document cannot be transmitted.**
        - Steps (e.)(1) and (e.)(2) above are followed.
        - When using a witness, documentation in the study trial records includes:

- a signed and dated attestation by the witness who participated on the call, that the patient confirmed their agreement to participate and signed and dated the informed consent document (or call recording); and
- a signed and dated attestation by the investigator/designee stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination by infectious material).

- Alternatively, in lieu of using a witness during the three-way telephone call or video conference, a recording of the conversation can be made and retained in the study record. Documentation in the trial records includes:
  - the recording of the conference call; and
  - a signed and dated attestation by the investigator/designee who participated on the call stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When either Method 1 or 2 is used to document informed consent, the resulting documentation should be: (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies), and (2) retained according to applicable FDA record retention requirements as part of the trial record.

If the patient is unable to provide informed consent and there is a legally authorized representative, investigators must obtain written consent from the

patient's legally authorized representative in accordance with 21 CFR 50.27(a).

16.3.4 From Whom May Consent/Assent be Obtained?

a. **Adults**

The ethical principle described in the Belmont Report, "Respect for Persons," directs that individuals should be treated as autonomous agents, meaning that potential research study participants must be given sufficient information to assure an informed decision about participation. In the U.S., adults (as defined by state law) may provide consent for themselves. In Ohio, adults are defined as persons aged 18 years or older.

NOTE: Investigators who conduct research in which adult participants are recruited at sites outside of the state of Ohio must follow laws applicable in the local jurisdiction which determine who is an adult, who may give legal consent, and how consent from adults who lack capacity should be obtained.

b. **Adults who Lack Capacity to Provide Informed Consent**

Individuals may lack capacity as a result of a range of cognitive disorders or conditions, which may result in the inability of individuals to protect themselves by freely-given informed consent. This vulnerable population is entitled to special protection in research.

An individual's consent capacity is not simply present or absent; capacity is best understood as occurring along a continuum. The term "incompetence" is similar to "incapacity", although incompetence has to do with legal matters while incapacity has to do with medical matters. Most states use "legally incapacitated" to refer to a person who cannot take care of his or her own physical safety and health.

PIs seeking to enroll adults who may lack capacity to make an informed decision must make clear in the IRB application how capacity to provide informed consent will be assessed. If participants are expected to lose the ability to consent while the study progresses, the research plan should address procedures for reassessing participants' ability to (1) understand protocol procedures, and (2) provide ongoing informed consent.

Incompetence may be a temporary result of the participant's condition (e.g., the participant is unconscious or sedated) or may

result from cognitive impairment produced by a disease or medical condition that impairs mental capacity. Whenever a participant lacks capacity to provide informed consent for him/herself, federal regulations require that the participant's legally authorized representative must give consent before the incapacitated person may participate in a research study.

For purposes of research conducted at The Christ Hospital, a legally authorized representative is an individual, judicial or other body authorized under applicable law to consent on behalf of a prospective subject in regard to the subject's participation in procedures involved in research. Usually, the law of the jurisdiction in which the research is conducted will be the state law where the research procedures will be performed.

Such consent may be obtained from:

1) A health care agent appointed by the potential subject in a Durable Power of Attorney for Healthcare (DAHC) or similar document
2) A court-appointed guardian
3) Next-of-kin in the following order of priority (unless otherwise specified in applicable law):
    i. Spouse
    ii. Adult child (18 years of age or older)
    iii. Parent
    iv. Adult sibling (18 years of age or older)
    v. Grandparent
    vi. Adult grandchild (18 years of age or older)

NOTE: The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes.

For individuals who know that they may lose capacity to provide consent during the course of the study, PIs should provide participants the opportunity to appoint a "research agent" who may provide consent on the participant's behalf after the participant loses capacity to consent for him/herself.

c. **Children**

All research projects involving children, regardless of funding source, will be reviewed and approved in accordance with 45 CFR Part 46, Subpart D, as applicable. Four categories of human research involving children may be approved by an Institutional Review Board (IRB). The four categories differ from one another according to the level of risk involved, the prospect of direct

benefit to research subjects, and the anticipated research findings. In all four categories, the proposed research activity must satisfy the requirements for parental or guardian permission and child assent (ref. HHS Research with Children FAQs). Depending on the category, additional conditions must be met in order for the IRB to approve the research activities.

1) **IRB-Approvable Categories**

i. **Research Not Involving Greater than Minimal Risk** (Ref. 45 CFR 46.404)

Research in which the IRB finds that no greater than minimal risk to children is presented may be conducated only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

ii. **Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subjects** (Ref. 45 CFR 46.405)

Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be conducted only if the IRB finds that:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

iii. **Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit To**

Individual Subjects, but Likely To Yield Generalizable Knowledge About The Subject's Disorder Or Condition (Ref. 45 CFR 46.406)

Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- The risk represents a minor increase over minimal risk;
- The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

iv. **Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate A Serious Problem Affecting The Health Or Welfare Of Children** (Ref. 45 CFR 45.407)

Research in which the IRB does not believe meets the requirements of 45 CFR 46 Sections 404, 405 or 406 may be conducted only if the IRB:

- Finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
- Has determined either:
    - That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or
    - The following:
        - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
        - The research will be conducted in accordance with sound ethical principles;
        - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

2) **Parental Permission: Requirements for Assent by Children and Permission by Parents or Guardians** (Ref. 45 CFR 46.408)

In addition to the determinations required under other applicable regulations of 45 CFR 46 Subpart D, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. Although children may be able to give their assent, they are unable to provide informed consent to participate in research. The IRB should determine that unless parental permission can be waived, adequate provisions are made for soliciting the permission of each child's parent(s) or legal guardian.

Definitions (ref. 45 CFR 46.402):

Children - 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.

Assent - A child's affirmative agreement to participate in research; mere failure to object should not, absent affirmative agreement, be construed as assent

Permission - The agreement of parent(s) or guardian to the participation of their child or ward in research

Parent - A child's biological or adoptive parent

Guardian - An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care

i. **Permission of Both Parents**
Permission should be obtained from both parents before a child is enrolled in research. However, the Institutional Review Board (IRB) may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 46.405. When research is covered by 45 CFR 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the care and custody of the child (ref. 45 CFR 46.408(b)).

ii. **Documentation of Parental Permission**
Parental permission should be documented in a manner similar to that used to document informed consent in accordance with and to the extent required by 45 CFR 46.117. An Institutional Review Board (IRB) may find that waiver of documentation of informed consent is appropriate under the HHS regulations at 45 CFR 46.117. When the IRB determines that assent is

required, it shall also determine whether and how assent must be documented.

iii. **Waiver of Parental Permission**
Under certain circumstances an IRB may waive the requirements for obtaining parental or guardian permission if it makes and documents the findings under 45 CFR 46.116(f)(3). In addition, if the IRB determines that the research 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), it may waive the consent requirements, provided an appropriate mechanism for protecting the children is substituted, and that the waiver is not inconsistent with Federal, state or local law. The 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. Ref. 45 CFR 46.408(c)

d. **Other Vulnerable Adult Populations**

TCH IRB recognizes that the ability of adult populations to give voluntary informed consent may be compromised by circumstance. Those circumstances range from economic or educational disadvantage, physical handicap, sedation, and drug abuse to the terminally ill. The research study protocol should take into account any of these issues and address them in the consent process.

e. **Pregnant Women, Fetuses, and Neonates**
Under federal regulations 45 CFR 46, Subpart B there are special conditions regarding involvement of pregnant women, fetuses or neonates in research. A pregnant woman must give her informed consent, and, if the research holds out the prospect of direct benefit only to the fetus, then the father must also give informed consent (unless he is unable to consent because of unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest). Each individual providing consent must be informed of the impact of the research on the fetus.

f. **Non-English Speakers**

Federal regulations require that researchers obtain the legally effective informed consent of the research subject or their legally authorized representative (if the subject is not able to consent for his/herself), and that informed consent shall be in language understandable to the subject or the representative *(45 CFR 46.116(a)(3))*. TCH IRB allows two means by which these requirements can be accomplished:

1) Written translation of IRB-approved documents, or
2) Use of a Short Form and request for an exception (45 CFR 46.117(b)(2); 21 CFR 50.27(b)(2))

As part of the IRB application process, the Principal Investigator must anticipate the need for written translations in considering the likely proportions of non-English-speaking people who may be encountered as eligible subjects for a proposed study. For instances of consenting an occasional and unexpected non-English-speaking subject in a study for which no consent form in the subject's language has been IRB-approved, the investigator must notify the IRB of the exception and utilize the IRB-approved short form consent in the subject's language and an interpreter to translate the consent form in the subject's language.

For purposes of research informed consent, an interpretation is a verbal exchange between two parties and the person serving as interpreter is fluent (can speak, read and write) in English and the language of the subject; a translation is the process of translating a written document (e.g., consent form) from one language into another, assuring the language of the translated document has the same meaning as the written document in the first language.

16.3.5 Determining a Participant's Understanding

In order for participation in a study to be truly voluntary, the participant must understand what he/she is agreeing to. The information should be presented to the participant in a way that is understandable to that participant. The investigator must ensure that the participant understands all elements of the consent form at the time the consent is signed, and also have means to assess the participant's continued understanding throughout the duration of the research study. It is important that the participant also understands that participation is voluntary, and that he/she can withdraw from the study at any time.

16.4 Basic Elements of Informed Consent

The Christ Hospital Institutional Review Board requires investigators to include the consent requirements established by HHS 45 CFR 46.116 and FDA regulations 21 CFR 50.20, as applicable, including providing each subject or the LAR:

16.4.1 A statement that the study involves research, an explanation of the purpose 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;

16.4.2 A description of any reasonably foreseeable risks or discomforts to the Subject;

16.4.3 A description of any benefits to the subject or to others that may reasonably be expected from the research;

16.4.4 A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

16.4.5 A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

16.4.6 For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

16.4.7 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;

16.4.8 A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled, and

16.4.9 One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

a. 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

b. 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.

16.4.10 Additional Elements of Informed

In addition, the consent document may contain the following items when appropriate:

a. 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;
b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;
c. Any additional costs to the subject that may result from participation in the research;
d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
e. 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;
f. The approximate number of subjects involved in the study;
g. 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;
h. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and
i. 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).

16.4.11 Research Subject to FDA Regulation

If the research is subject to FDA regulation, a there must also be a statement noting the possibility that the FDA may inspect study records. Research is FDA regulated if it involves the use of any drugs or medical devices other than the use of approved drugs or medical devices in the course of medical practice, or if the data will be submitted to or held for inspection by the FDA. (Ref. 21 CFR 50.25(a)(5))

The above elements are included in the preprinted "boilerplate" text of the TCH IRB informed consent template.

16.4.12 HIPAA Authorization

HIPAA requires a participant's prior written authorization before his or her identifiable health information can be used or disclosed by “covered entities.” HIPAA authorization for use and disclosure of health information is included in the "boilerplate" text of the TCH IRB informed consent template.

16.4.13IRB Approval of Informed Consent Documents

The IRB must review and approve all materials associated with obtaining informed consent.