1.0 Purpose:

1.1 When a proposed research study involves children, the Hartford HealthCare (HHC) Institutional Review Board (IRB) must take into consideration the special regulatory requirements set forth in 45 CFR 46, Subpart D that provide additional protection for the children who would be involved in the research. If the proposed research involves products regulated by the U.S. Food and Drug Administration (FDA), the parallel regulations at 21 CFR 50 will be applied.

1.2 The concepts of minimal risk, minor increase over minimal risk, prospect of direct benefit, assent, and permission are the basis of this special protection. The purpose of this policy, therefore, is to provide a framework to ensure that pediatric studies are conducted ethically.

2.0 Definitions:

2.1 **Assent** - is a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

2.2 **Children**

2.2.1.1 For the purpose of applying DHHS regulations (45 CFR 46 Subpart D) and FDA regulations (21 CFR 50 Subpart D), children are ***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.***

2.2.1.2 Connecticut law defines individuals less than 18 years of age to be minors (C.G.S. Section 1-1(d)), and thus children as defined in federal regulation. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, the HHC IRB defines children as persons less than eighteen years of age.

2.2.1.3 Connecticut law, however, provides minors with "majority" status in some circumstances, giving them the right to consent to their own medical care, as follows:

2.2.1.3.1 **Emancipated minors** (Connecticut law enumerates certain categories of individuals age 16 or older who may initiate procedures to have the right to make medical decisions on their own behalf, such as a minor who has been married; is active duty; willingly lives apart from parents and manages own financial affairs, etc.; (C.G.S. Section 46b-150(b)). Emancipated individuals do not meet the federal definition of children and therefore Subpart D requirements do not apply;

2.2.1.3.2 Minors seeking medical care for certain conditions specified in state law may consent to participate in research if the research is limited to the categories noted below; in such circumstances the individuals are not considered children and therefore Subpart D is not applicable:

- All individuals under 18 years of age, if the research procedures are limited to: HIV testing, counseling, and treatment (19a-582; 19a-592); outpatient mental health services (19a-14c); testing or treatment for sexually transmitted diseases (19a-216); treatment or rehabilitation for alcohol or drug dependence (17a-688); abortion counseling and treatment (19a-602); or consenting to medical care for a child (19a-285);

- All individuals 14 years of age or older, if the research procedures are limited to inpatient mental health services (17a-79) (parents must be notified of admission within 5 days);

- All individuals 17 years of age, if the research procedures are limited to donation of blood or any component thereof and to the withdrawal of blood in conjunction with any voluntary blood donation program (19a-285a).

2.2.1.4 To the extent that Connecticut law does not specifically address consent of children with majority status to research, the HHC IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis, and will seek guidance from the General Counsel as needed.

2.3 **Guardian**

2.3.1.1 Under DHHS regulations "guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

2.3.1.2 Under FDA regulations "guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. A guardian may grant permission for a child to participate in research.

2.3.1.3 In Connecticut a “Guardian” of a minor means the duty and authority to act in the best interests of the minor, and includes the obligation of care and control, and the authority to make major decisions affecting the minor’s education and welfare (C.G.S 45a-604(5)).

2.4 **Legally Authorized Representative (LAR) -** an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to

the subject's participation in the procedure(s) involved in the research. For purposes of this policy, a LAR for children includes a parent or court-appointed legal guardian. In almost all cases at HHC, when the research involves children, the parent (or other legal guardian) is the LAR.

2.5 **Parent** - means a child's biological or adoptive parent.

2.6 **Permission** - means the agreement of parent(s) or guardian to the participation of their child or ward in research.

2.7 **Ward** – means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

3.0 Procedure:

3.1 When reviewing research with children as subjects, in addition to ensuring adherence to the general regulatory requirements of 45 CFR 46, Subpart A, the IRB will also consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB will consider the circumstances of the children to be enrolled in the study, for example their health status, age, and ability to understand what is involved in the research, as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

3.2 The exemptions at 45 CFR 46.104(d)(1), (4), (5), (6), (7), and (8) may be applied to research subject to subpart D if the conditions of the exemption are met. Exemptions at 45 CFR 46.104(d)(2)(i) and (ii) only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. The exemption at 45 CFR 46.104(d)(2)(iii) may not be applied to research subject to subpart D.

3.3 When reviewing research involving children, the IRB will include one or more members who are knowledgeable about and experienced in working with children. The IRB member or consultant, if applicable, will be knowledgeable in pediatric ethical, clinical, and psychosocial issues.

3.4 DHHS regulations limit research involving children to those activities that meet one of four categories of research. These categories are based on the level of risk and potential for benefit to the individual participant.

3.4.1 **Research not involving greater than minimal risk to the children (45 CFR 46.404, 20 CFR 50.51)**

3.4.1.1 To approve this category of research, the IRB must make the following determinations:

- the research presents no greater than minimal risk to the children; ***and***
- adequate provisions are made for soliciting the assent of the children and the permission of one or both of their parents or guardians.

3.4.2 **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research (45 CFR 46.405, 20 CFR 50.52).**

3.4.2.1 To approve research in this category, the IRB must make the following determinations:

- the risk is justified by the anticipated benefits to the subjects;
- the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; ***and***
- adequate provisions are made for soliciting the assent of the children and the permission of one or both of their parents or guardians.

3.4.3 **Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition (45 CFR 46.406, 20 CFR 50.53).**

3.4.3.1 In order to approve research in this category, the IRB must make the following determinations:

- the risk of the research represents a minor increase over minimal risk;
- the intervention or procedure presents experiences to the child 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 subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; ***and***
- adequate provisions are made for soliciting the assent of the children and the permission of both parents or guardians, unless one parent is deceased, unknown, incompetent, or *not reasonably available or when one parent has legal responsibility for the care and custody of the child subject.

***Not reasonably available:**
Means the other parent is not contactable by phone, mail, email or fax or the other parent's whereabouts are unknown.
Does not mean the other parent is at work, at home, lives in another city, state or country, but is contactable by phone, mail, email or fax.

Examples of not reasonably available:

- The other parent is on active military duty and is not contactable by phone, mail, email or fax.
- The other parent is incarcerated and is not contactable by phone, mail, email or fax.
- The whereabouts of the other parent are unknown

3.4.4 **Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 20 CFR 50.54).**

3.4.4.1 If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to the Department of Health & Human Services (DHHS) for review. The research may proceed only if the Secretary of DHHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) 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; ***and***
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in DHHS regulations at 45 CFR 46.408.

3.5 **Requirements for Permission by Parents or Guardians and Assent by Children**

3.5.1 The Federal regulations delineate specific requirements for obtaining **permission from parents** or legal guardians that are based on the level of risk and potential for benefit to the individual participant. The investigator must make adequate provisions for soliciting the permission of each child's parents or legal guardian as determined by the IRB (45 CFR 46.408(b), and 21 CFR 50.55(e) if applicable).

3.5.1.1 For research to be conducted under 45 CFR 46.404 or 20 CFR 50.51, where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research in this category.

3.5.1.2 For research to be conducted under 45 CFR 46.405 or 20 CFR 50.52, where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research in this category.

3.5.1.3 For research to be conducted under 45 CFR 46.406 or 20 CFR 50.53, where parental permission is to be obtained, the IRB will find that **both parents** must give 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 child.

3.5.1.4 For research to be conducted under 45 CFR 46.406 or 20 CFR 50.53, where parental permission is to be obtained, the IRB will find that **both parents** must give 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 child

3.5.1.5 Parental permission must be documented by the use of a written consent form approved by the IRB and signed and dated by the parent(s).

3.5.2 For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver under 45 CFR 46.116(d), ***or***
- The IRB determines that the research protocol is designed for conditions or 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 an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal State, or local law. 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.

3.5.2.1 Waiver of parental permission is not permitted for research covered by the FDA regulations.

3.5.3 When, in the judgment of the IRB, the children involved in the research are capable of providing assent, the IRB will determine that adequate provisions are made for soliciting the **assent of the children**.

3.5.3.1 Because “assent” means a child’s affirmative agreement to participate in research, 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 has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

3.5.3.2 The IRB will take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand more closely resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent/parental permission by adults. For children whose age and maturity level limits their ability to fully

comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

3.5.3.3 The DHHS regulations do not require documentation of assent. Rather, 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 should decide what form of documentation, if any, is most appropriate.

3.5.3.3.1 The HHC IRB believes that children ages 7 and older should be given an opportunity to provide assent. If young children are involved who are unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. Typically, oral assent using an IRB-approved script will be documented by notation in the study record of the verbal agreement. The IRB may also decide that documentation of assent is not warranted.

3.5.3.3.2 Generally, written assent should be obtained from children 7 - 12 years of age using a simple one-page assent form.

3.5.3.3.3 If adolescents (ages 13-17) are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent's assent. The HHC IRB would typically allow the parental permission form to be written at a 6^{th}-8^{th} grade level with a signature line for both parental permission and the signature of the child to be used (given the subject's intellectual capabilities fall within the range of a normal 13-17 year old).

3.5.3.4 When writing assent forms and scripts that are age-appropriate, researchers should take into account the typical child's experience and level of understanding. The document should be written such that it describes not only the essential elements of the study, but conveys respect and dignity for the child.
The assent form should:
3.5.3.4.1 tell why the research is being conducted;
3.5.3.4.2 describe what will happen and for how long or how often;

3.5.3.4.3 say it's up to the child to decide if they want participate, that it's okay to say no, and that they can stop at any time if they wish;
3.5.3.4.4 explain if it will hurt and if so for how long and how often;
3.5.3.4.5 say what the child's other choices are;
3.5.3.4.6 describe any good things that might happen;
3.5.3.4.7 say whether there is any compensation for participating;
3.5.3.4.8 ask for questions.

3.5.3.5 At times there may be disagreement between a child and his/her parent's about research participation. If the child is capable of assent and the IRB requires that assent be sought, and the child dissents from participating, even if his or her parents or guardians have granted permission, the child's decision prevails.

3.5.3.6 **The IRB may <u>waive</u> assent requirements** under the following circumstances:

- The IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted;
- 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 <u>and</u> is only available in the context of the research
- If the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults as specified in 45 CFR 46.116 (c) or (d) or 21 CFR 50.55(d).

3.5.3.7 **When a child who was enrolled in research with parental or guardian permission subsequently reaches age 18 years**, the legal age of consent to the procedures involved in ongoing research, the subject's participation in the research is no longer regulated by the requirements of this policy or by 45 CFR 46.408 or 21CFR 50.55 regarding parental or guardian permission and subject assent. Unless the IRB determines that the requirements for obtaining informed consent can be waived, the investigator is expected to seek and obtain the legally effective informed consent, as described in 45 CFR 46.116 and 21 CFR 50.20 and .25, for the now-adult subject for any ongoing interactions or interventions with the subjects.

3.6 Research Involving Wards of the State

3.6.1 Children who are wards of the State or any other agency, institution, or entity can be included in research that is to be conducted categories under 45 CFR 46.<u>404</u> (20 CFR 50.51) or 45 CFR 46.<u>405</u> (20 CFR 50.52).

3.6.2 **However**, wards may be included in research to be conducted under category 45 CFR 46.406 (20 CFR 50.53) - research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition - **only if** such research is:

- related to their 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.

3.6.2.1 If the research meets the above condition(s), an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in loco parentis.

3.6.2.2 The advocate 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 and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

3.6.3 Permission must be obtained and documented from the ward's legal guardian as for other children. It is important to note, however, that foster parent cannot provide permission because they are not considered legal guardians. In most cases, the protective services worker or state-appointed case worker that stands in loco parentis for these children.

3.6.4 Research protocols that plan to include children who are wards of the State of Connecticut must obtain approval from the Connecticut Department of Children and Families (DCF) IRB. For more information about how to submit to the DCF IRB, visit http://www.ct.gov/dcf/cwp/view.asp?a=2555&q=314538 .

3.6.4.1 Similarly, if a currently enrolled subject becomes a ward of the state during the course of their participation in the study, the HHC IRB should be notified and the investigator must seek DCF IRB approval.

4.0 Documentation:

4.1 The IRB shall prepare and maintain adequate documentation of IRB activities related to research reviewed under DHHS regulations at 45 CFR 46 – Subpart D and. Minutes will document the category under which the protocol is approved, as well as determinations specific to parental permission (whether one or two-parent permission is required), assent, or waiver of consent and/or inclusion of wards.

4.2 The HRPP office will maintain documentation related to IRB review of studies conducted under Subpart D, including initial submissions, continuing reviews, and modifications, as well as reports of unanticipated problems, complaints, deviations, non-compliance, and correspondence related to review of such items, as well as

checklists pertinent to the reviews, for a minimum of 6 years after completion of the study.

5.0 References:

5.1 45 CFR 46 Subpart D – Additional Protections for Children Involved as Subjects in Research (45 CFR 46.401, 402, 403, 404, 405, 406, 407, 408, and 409)

5.2 45 CFR 46.104(b)(3)

5.3 21 CFR 50 Subpart D – Additional Safeguards for Children in Clinical Investigations (21 CFR 50.50, 51, 52, 53, 54, 55, and 56)

5.4 OHRP Research with Children Frequently Asked Questions (http://answers.hhs.gov/ohrp/categories/1570)

5.5 OHRP "Information on Special Protections for Children as Research Subjects" (http://www.hhs.gov/ohrp/policy/populations/children.html)

5.6 OHRP "Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process" (http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html)

5.7 FDA Guidance for Industry - E11 Clinical Investigation of Medicinal Products in the Pediatric Population (December 2000)

5.8 Protections for Children in Research: A Report to Congress in Accord with Section 1003 of P.L. 106-310, Children's Health Act of 2000 (May 2001)

5.9 State of Connecticut Department of Children and Families - Policy 26-8-1 (Institutional Review Board) - http://www.ct.gov/dcf/cwp/view.asp?a=2639&Q=393382

5.10 Institutional Review Board Management and Function, Bankert, E. A., Amdur, R. J., 2nd Edition, 2006

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	CLB	7/1/11	Conversion to new policy template; general expansion of policy
02	CLB	10/6/14	Added clarification and definition of "not reasonably available" in Section 3.4.3.1
03	CLB	3/15/20	Update Section 3.2 to describe the exemption categories that may and may not be applied to research subject to Subpart D per the Revised Common Rule

Element II.4.A. and III.1.C.