

Connecticut Children’s Medical Center

Human Research Protection Program

Standard Operating Procedures

September 3, 2026

1	HUMAN RESEARCH PROTECTION PROGRAM (HRPP)	8
1.1	POLICY	8
1.2	MISSION:	8
1.3	INSTITUTIONAL AUTHORITY	9
1.4	DEFINITIONS	9
1.5	ETHICAL PRINCIPLES	12
1.6	REGULATORY COMPLIANCE	12
1.7	FEDERALWIDE ASSURANCE (FWA)	13
1.8	RESEARCH COVERED BY THE HRPP	13
1.9	WRITTEN POLICIES AND PROCEDURES	14
1.10	HRPP ORGANIZATION	15
1.10.1	<i>Institutional Official</i>	15
1.10.2	<i>Medical Director of the HRPP</i>	15
1.10.3	<i>Director of the HRPP</i>	17
1.10.4	<i>Institutional Review Board (IRB)</i>	18
1.10.5	<i>Legal Department</i>	18
1.10.6	<i>Division/Department Heads</i>	19
1.10.7	<i>The Investigator</i>	19
1.10.8	<i>Other Related Units</i>	19
1.10.9	<i>Relationship between Components</i>	21
1.11	HRPP OPERATIONS	22
1.11.1	<i>HRPP Office</i>	22
1.11.2	<i>Sr. IRB Manager</i>	22
1.11.3	<i>IRB Coordinator/Analyst</i>	23
1.11.4	<i>IRB Operations Manager</i>	23
1.11.5	<i>Selection, Supervision and Evaluation of HRPP Supporting Staff</i>	23
1.12	HRPP RESOURCES	24
1.13	QUALITY IMPROVEMENT/QUALITY ASSURANCE	25
1.13.1	<i>Institutional Periodic (“Not for Cause”) and Directed (“For Cause”) Reviews</i>	25
1.13.2	<i>Non- Institutional Directed Reviews and Compliance Reviews</i>	26
1.13.3	<i>Reporting and Disposition</i>	26
1.13.4	<i>Conduct of Quality Assurance/Quality Improvement Activities for IRB Operations (IRB Internal Compliance Reviews)</i>	26
1.13.5	<i>Additional Quality Improvement Activities</i>	29
1.14	COLLABORATIVE RESEARCH PROJECTS	30
	<i>Background</i>	30

<i>Policy Statement</i>	30
1.15 IRB RELIANCE MECHANISMS	31
1.15.1 Connecticut Children's IRB Reliance on an External IRB.....	31
1.15.2 Another Institution's Reliance on the Connecticut Children's IRB	33
1.15.3 Serving as IRB of Record for an Entity Without an IRB.....	35
1.15.4 Serving as IRB of Record for a Non-Affiliated Individual Investigator.....	35
1.15.5 Research Reviewed by the National Cancer Institute (NCI) Pediatric Central IRB (CIRB)	35
1.15.6 Collaborative Research at both Connecticut Children's and a Neighboring Institution	36
2 INSTITUTIONAL REVIEW BOARD	37
2.1 P O L I C Y	37
2.2 I R B AUTHORITY	38
2.3 NUMBER OF IRBs.....	38
2.4 ROLES AND RESPONSIBILITIES.....	38
2.4.1 Chairperson of the IRB.....	38
2.4.2 Vice Chair of the IRB.....	39
2.4.3 Subcommittees of the IRB	39
2.5 IRB MEMBERSHIP.....	40
2.6 COMPOSITION OF THE IRB	41
2.7 APPOINTMENT OF MEMBERS TO THE IRB.....	42
2.8 A L T E R N A T E MEMBERS.....	42
2.9 IRB MEMBER CONFLICT OF INTEREST	42
2.10 USE OF CONSULTANTS.....	43
2.11 DUTIES OF IRB MEMBERS.....	44
2.12 ATTENDANCE REQUIREMENTS	44
2.13 TRAINING / ONGOING EDUCATION OF CHAIR AND IRB MEMBERS IN REGULATIONS, PROCEDURES.....	45
2.13.1 Research funded by the Department of Defense.....	46
2.14 LIABILITY COVERAGE FOR IRB MEMBERS	46
2.15 REVIEW OF IRB MEMBER PERFORMANCE	46
2.16 REPORTING AND INVESTIGATION OF ALLEGATIONS OF UNDUE INFLUENCE.....	47
3 IRB REVIEW PROCESS.....	47
3.1 P O L I C Y	47
3.2 D E F I N I T I O N S	47
3.3 HUMAN SUBJECTS RESEARCH DETERMINATION	48
3.3.1 Quality Improvement Projects.....	48
3.4 E X E M P T STUDIES	49
3.4.1 Limitation on Research Subjects:.....	50
3.4.2 Categories of Exempt Research.....	50
3.4.3 FDA Exemptions	55
3.4.4 Additional Protections	55
3.5 E X P E D I T E D REVIEW.....	56
3.5.1 Categories of Research Eligible for Expedited Review.....	56
3.5.2 Expedited Review Procedures	60
3.5.3 Informing the IRB	61
3.6 C O N V E N E D IRB MEETINGS.....	61
3.6.1 IRB Meeting Schedule	61
3.6.2 Preliminary Review	61

3.6.3 Primary and Secondary Reviewers.....	62
3.6.4 Pre-Meeting Distribution of Documents.....	62
3.6.5 Materials received by the IRB.....	63
3.6.6 Quorum	63
3.6.7 Meeting Procedures.....	64
3.6.8 Guests.....	64
3.7 CRITERIA FOR IRB APPROVAL OF RESEARCH	65
3.7.1 Risk/Benefit Assessment	66
3.7.2 Selection of subjects is equitable.....	67
3.7.3 Informed Consent.....	68
3.7.4 Data Safety Monitoring	68
3.7.5 Privacy and Confidentiality.....	69
3.7.6 Vulnerable Populations	70
3.8 ADDITIONAL CONSIDERATIONS DURING IRB REVIEW AND APPROVAL OF RESEARCH	70
3.8.1 Determination of Risk.....	70
3.8.2 Period of Approval.....	71
3.8.3 Independent Verification That No Material Changes Have Occurred.....	72
3.8.4 Consent Monitoring	72
3.8.5 Investigator Conflicts of Interest.....	73
3.8.6 Significant New Findings.....	73
3.8.7 Advertisements.....	73
3.8.8 Payment to Research Subjects.....	75
3.8.9 Recruitment Incentives.....	75
3.8.10 Compliance with all Applicable State and Local Laws.....	75
3.9 POSSIBLE IRB ACTIONS.....	76
3.10 STUDY SUSPENSION, TERMINATION AND ADMINISTRATIVE HOLD.....	77
3.10.1 Suspension/Termination.....	77
3.10.2 Administrative Hold	78
3.10.3 Protection of Currently Enrolled Participants	79
3.11 CONTINUING REVIEW	80
3.11.1 Approval Period.....	80
3.11.2 Continuing Review Process	81
3.11.3 Expedited Review of Continuing Review.....	83
3.11.4 What Occurs if There is a Lapse in Continuing Review?	83
3.12 AMENDMENT OF AN APPROVED PROTOCOL.....	84
3.12.1 Expedited Review of Protocol Modifications.....	85
3.12.2 Full Board Review of Protocol Modifications	85
3.13 CLOSURE OF PROTOCOLS	86
3.14 REPORTING IRB ACTIONS.....	86
3.15 APPEAL OF IRB DECISIONS	86
4 DOCUMENTATION AND RECORDS.....	87
4.1 POLICY	87
4.2 IRB RECORDS	87
4.3 IRB MEMBERSHIP ROSTER	88
4.4 THE IRB MINUTES	89
4.5 DOCUMENTATION OF EXEMPTIONS	91
4.6 DOCUMENTATION OF EXPEDITED REVIEWS.....	91

4.7 RECORD RETENTION	91
4.8 INVESTIGATOR RECORDS	92
4.8.1 <i>FDA Regulated Studies</i>	92
4.8.2 <i>Federally Funded Studies</i>	94
4.8.3 <i>Studies subject to the Health Insurance Portability and Accountability Act (HIPAA)</i>	94
5 OBTAINING INFORMED CONSENT/PARENTAL PERMISSION/ASSENT TO PARTICIPATE IN RESEARCH	94
5.1 POLICY	95
5.2 DEFINITIONS	95
5.3 BASIC REQUIREMENTS	97
5.4 RESEARCH WITH CHILDREN	97
5.5 INFORMED CONSENT/PARENTAL PERMISSION PROCESS	98
5.6 ELEMENTS OF INFORMED CONSENT/PARENTAL PERMISSION	100
5.7 ALLOWABLE CATEGORIES FOR RESEARCH INVOLVING CHILDREN	103
5.7.1 <i>Allowable Categories</i>	103
5.7.2 <i>Assent from Children</i>	106
5.7.3 <i>The Assent Form</i>	107
5.8 CHILDREN WHO ARE WARDS	107
5.9 DOCUMENTATION OF INFORMED CONSENT.....	108
5.10 CONSENT MONITORING	110
5.11 WAIVER OF INFORMED CONSENT	111
5.12 WAIVER OF DOCUMENTATION OF INFORMED CONSENT	112
5.13 SUBJECT WITHDRAWALS FROM CLINICAL TRIALS	113
5.14 POSTING OF CLINICAL TRIAL CONSENT FORMS.....	114
6 ADDITIONAL PROTECTIONS FOR SUBJECT POPULATIONS IN RESEARCH	114
6.1 POLICY	114
6.2 DEFINITIONS	114
6.3 INVOLVEMENT OF SUBJECT POPULATIONS.....	115
6.4 RESPONSIBILITIES.....	116
6.5 PROCEDURES	117
6.6 RESEARCH INVOLVING PREGNANT WOMEN, HUMAN FETUSES AND NEONATES	117
6.6.1 <i>Research Involving Pregnant Women or Fetuses</i>	117
6.6.2 <i>Research involving neonates</i>	119
6.6.3 <i>Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material</i>	121
6.6.4 <i>Research Not Otherwise Approvable</i>	121
6.7 RESEARCH INVOLVING PRISONERS.....	121
6.8 ADULT SUBJECTS WITH IMPAIRED DECISION-MAKING CAPACITY	121
6.8.1 <i>IRB composition</i>	123
6.8.2 <i>Determination of Decision-Making Capacity</i>	123
6.8.3 <i>Informed Consent and Assent</i>	125
6.8.4 <i>Surrogate Consent (Adult Subjects)</i>	126
7 INVESTIGATIONAL DRUGS & DEVICES	128
7.1 POLICY	128
7.2 DEFINITIONS	128
7.3 FDA EXEMPTIONS	130

7.4 IND/IDE REQUIREMENTS.....	130
7.4.1 IND Exemption.....	131
7.4.2 Exempted IDE Investigations.....	132
7.5 RESPONSIBILITIES.....	132
7.5.1 PI.....	133
7.5.2 IRB.....	135
7.6 EMERGENCY USE	136
7.6.1 Emergency Exemption from Prospective IRB Approval.....	136
7.6.2 Emergency Use of a Drug or Biologic.....	136
7.6.3 Emergency Use of a Device.....	138
7.7 EXPANDED ACCESS OF INVESTIGATIONAL DRUGS & DEVICES	139
7.7.1 Expanded Access of Investigational Drugs.....	140
7.7.2 Expanded Access of Investigational Devices	142
7.7.3 IRB Review of Individual Expanded Access of Drugs & Devices	143
7.8 PLANNED EMERGENCY RESEARCH	144
7.9 HUMANITARIAN USE DEVICES (HUD)	144
8 REPORTABLE NEW INFORMATION	144
8.1 POLICY.....	144
8.2 DEFINITIONS	145
8.3 PROCEDURES	146
8.3.1 Reporting to the IRB.....	146
8.3.2 Timelines for Reporting to the IRB	148
8.3.3 IRB Review Process.....	148
8.3.4 Reconsideration of the IRB Decision	150
9 COMPLAINTS AND NON-COMPLIANCE.....	150
9.1 POLICY	150
9.2 COMPLAINTS	151
9.3 NON-COMPLIANCE.....	151
10 REPORTING TO REGULATORY AGENCIES AND INSTITUTIONAL OFFICIALS.....	151
10.1 POLICY	152
10.2 PROCEDURES	152
11 INVESTIGATOR RESPONSIBILITIES	154
11.1 POLICY	154
11.2 INVESTIGATORS	154
11.3 RESPONSIBILITIES.....	155
11.4 TRAINING / ONGOING EDUCATION OF INVESTIGATORS AND RESEARCH TEAM	156
11.4.1 Orientation	156
11.4.2 Initial Education	157
11.4.3 Continuing Education and Recertification.....	158
11.4.4 Additional Resources	158
11.5 INVESTIGATOR CONCERNS	158
12 SPONSORED RESEARCH.....	159
12.1 POLICY	159

12.2 DEFINITIONS.....	159
12.3 RESPONSIBILITY.....	159
13 CONFLICT OF INTEREST IN RESEARCH.....	160
13.1 POLICY	160
13.2 DEFINITIONS.....	161
13.3 INDIVIDUAL CONFLICTS OF INTEREST	163
13.3.1 <i>Investigator Responsibilities:</i>	163
13.3.2 <i>Institutional Review Procedures for Disclosures:</i>	164
13.3.3 <i>Requirements specific to PHS-funded research</i>	167
13.3.4 <i>Conflict of Interest Training Requirements for Investigators</i>	169
13.3.5 <i>Maintenance of Records</i>	169
13.3.6 <i>Sanctions</i>	170
14 PARTICIPANT OUTREACH	170
14.1 POLICY	170
14.2 RESPONSIBILITY.....	171
14.3 OUTREACH RESOURCES AND EDUCATIONAL MATERIALS	171
14.4 EVALUATION.....	171
15 HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA).....	172
15.1 POLICY	172
15.2 DEFINITIONS	172
15.3 HISTORICAL BACKGROUND	174
15.4 EFFECTS OF HIPAA ON RESEARCH	174
15.5 RESEARCH UNDER HIPAA	175
15.5.1 <i>Waiver of Authorization for Use or Disclosure of Protected Health</i>	175
<i>Information in Research</i>	175
15.5.2 <i>Review Preparatory to Research</i>	176
15.5.3 <i>Research on Protected Health Information of Decedents</i>	178
15.5.4 <i>Limited Data Sets with a Data Use Agreement</i>	178
15.6 HIPAA AND DOCUMENTATION REQUIREMENTS.....	179
15.7 PATIENT RIGHTS AND RESEARCH.....	180
15.8 HIPAA AND EXISTING STUDIES	180
15.9 WAIVERS TO HIPAA CONSENT FORM.....	180
16 SPECIAL TOPICS.....	180
16.1 CERTIFICATE OF CONFIDENTIALITY	180
16.1.1 <i>Statutory Basis for Protection</i>	181
16.1.2 <i>Usage</i>	181
16.1.3 <i>Limitations</i>	182
16.1.4 <i>Application Procedures</i>	182
16.2 GENETIC STUDIES	183
16.3 RESEARCH INVOLVING CODED PRIVATE INFORMATION OR BIOLOGICAL SPECIMENS.....	183
16.3.1 <i>Who Should Determine Whether Coded Private Information or Specimens</i>	185
<i>Constitutes Human Subjects Research</i>	185
16.4 CASE REPORTS REQUIRING IRB REVIEW	185
16.4.1 <i>Definitions</i>	185

16.5 MANDATORY REPORTING	185
16.6 CONNECTICUT CHILDREN’S EMPLOYEES AND STUDENTS AS SUBJECTS.....	186
16.7 STUDENT RESEARCH	187
16.7.1 <i>Individual Research Projects Conducted by Students</i>	187
16.7.2 <i>Independent Study, Theses and Dissertations</i>	187
16.8 ORAL HISTORY	187
16.9 TRANSNATIONAL RESEARCH.....	188
16.9.1 <i>Knowledge of Local Laws</i>	188
16.9.2 <i>Knowledge of Local Research Context</i>	189
16.9.3 <i>Qualifications of Researchers and Research Staff</i>	189
16.9.4 <i>Continuing Review and Review of Modifications to Previously Approved</i>	189
<i>Research</i>	189
16.9.5 <i>Handling of complaints, non-compliance, and unanticipated problems involving risks to</i> <i>participants or others</i>	190
16.9.6 <i>Coordination and communication with local IRB or ECs when appropriate</i>	190
16.9.7 <i>Additional Requirements</i>	191
16.9.8 <i>Monitoring of Approved Transnational Research:</i>	191
16.9.9 <i>Independent Participating Transnational Research Sites</i>	191
APPENDIX A: RESEARCH INVOLVING PRISONERS	192
A.1 APPLICABILITY.	192
A.2 MINIMAL RISK	193
A.3 COMPOSITION OF THE IRB [45 CFR 46.304].....	194
A.4 ADDITIONAL DUTIES OF THE IRB [45 CFR 46.305]	194
A.5 WHEN A SUBJECT BECOMES A PRISONER	195
A.6 WAIVER FOR EPIDEMIOLOGY RESEARCH	196
APPENDIX B: DEPARTMENT OF DEFENSE (DOD)-FUNDED RESEARCH	197
B. 1 DEFINITIONS	197
B.2 SPECIFIC CONSIDERATIONS	197
<i>Scientific Review</i>	197
<i>Education Requirements</i>	197
<i>Greater than Minimal Risk Studies: Research Monitor Required</i>	198
<i>Vulnerable Populations</i>	198
<i>Classified Research</i>	199
<i>Additional Protections for Military Personnel</i>	199
<i>Informed Consent Process</i>	199
<i>Limitations on Waiver of Consent</i>	200
<i>Additional Investigator Responsibilities</i>	200
<i>International Research</i>	200
APPENDIX C: RESEARCH CONDUCTED IN SCHOOLS	202
<i>Definitions</i>	202
<i>Procedures</i>	202
APPENDIX D: RESEARCH SUBJECT TO ENVIRONMENTAL PROTECTION AGENCY (EPA) REQUIREMENTS.....	205
APPENDIX E: PLANNED EMERGENCY RESEARCH.....	206
APPENDIX F: HRPP EMERGENCY PREPAREDNESS PLAN	211

<i>Institutional Responsibilities</i>	<i>211</i>
<i>HRPP Responsibilities</i>	<i>211</i>
<i>Research Team Responsibilities.....</i>	<i>212</i>
<i>HRPP/IRB Staffing Levels.....</i>	<i>212</i>
<i>Electronic Systems.....</i>	<i>212</i>
<i>IRB Committee Functions</i>	<i>213</i>
<i>Responses to Emergency</i>	<i>213</i>
<i>Training.....</i>	<i>214</i>
<i>Communication</i>	<i>215</i>
<i>Investigator Considerations.....</i>	<i>215</i>

1 Human Research Protection Program (HRPP)

1.1 Policy

Connecticut Children's Medical Center (Connecticut Children's) fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of Connecticut Children's. In the review and conduct of research, actions by Connecticut Children's will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the Ethical Principles and Guidelines for the Protection of Human Subjects of Research (often referred to as the Belmont Report). The actions of Connecticut Children's will also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this policy, Connecticut Children's has established a human research protection program (HRPP).

1.2 Mission:

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide high quality education to the research community,
- Provide timely and high quality review of human subject research and monitoring of human research projects; and
- Facilitate excellence in human subjects' research. The HRPP includes mechanisms to:
- Establish a formal process to monitor, evaluate and continually improve the protection

of human research participants.

- Dedicate resources sufficient to carry out the HRPP's mission.
- Exercise oversight of research protection activities.
- Educate investigators and research staff about their ethical responsibility to protect research participants.
- When appropriate, intervene in research and respond directly to concerns of research participants.

1.3 Institutional Authority

The Human Research Protection Program operates under the authority of Connecticut Children's organizational policy "Human Research Subject Protection Program (HRPP)", approved by the Corporate Board of Directors in November 2008. As stated in that policy, the "IO and HRPP office shall adopt operating procedures ... that shall serve as the governing procedures for the conduct and review of all human subject research conducted under the auspices of CONNECTICUT CHILDREN'S." The HRPP Policy and these operating procedures are made available to all investigators and research staff and are posted on the Connecticut Children's intranet.

1.4 Definitions

Common Rule. The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Research Involving Human Participants – means any activity that meets the definition of "research" and involves "human subjects" as defined by either the Common Rule (45 CFR 46.102(e)) or FDA regulations.

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator (whether professional or student) conducting research:

- o Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- o Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

(With the implementation of the Common Rule, the Newborn Dried Blood Spots Act of 2014 which required that the secondary use of newborn dried blood spots be considered human subjects' research, no longer applies)

Intervention means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction means communication or interpersonal contact between investigator and subject.

Private information means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record).

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

An **identifiable biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

For research covered by FDA regulations (21 CFR 50 and 56), human subject means an individual who is or becomes a participant in a clinical investigation (as defined below), either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject/participant also includes any individual on whose tissue specimen an investigational device is used or tested. *When medical device research involves in vitro diagnostics and unidentified tissue specimens, unidentified tissue specimens are defined as human subjects.*

Note: The terms "subject" and "participant" are used interchangeably in this document and have the same definition.

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge.

For the purposes of this policy, a "**systematic investigation**" is an activity that involves a prospective plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The following activities are deemed not to be research:

(1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Research as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]
- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]
- Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]”

Test Article. A test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

Institutional Review Board (IRB). An IRB is a board designated by Connecticut Children's to review, to approve the initiation of, and to conduct periodic review of research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The IRB may be assigned other review functions as deemed appropriate.

Protocol. The protocol includes the complete packet of materials submitted to the IRB for review, including a description of the research design and methodology as well a complete description of the procedures for the protection of human participants in the research.

Clinical Trial. A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

1.5 Ethical Principles

Connecticut Children's is committed to conducting research with the highest regard for the welfare of human subjects. It upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

- 1) **Respect for Persons**, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- 2) **Beneficence**, which is assured by ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
- 3) **Justice**, the equitable selection of subjects.

These principles are also the expected obligations of the entire research community including researchers, research staff, IRB members, the IRB Chair, the Institutional Official, employees and students. The Human Research Protection Program (HRPP), in partnership with its research community is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

1.6 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and institutional policies. All human subjects' research at Connecticut Children's conducted or supported by DHHS or federal agencies that have adopted the Common

Rule is conducted in accordance with the policy and regulations found in the Common Rule, 21 CFR 50 and 56, and all other applicable federal, state, and local laws and regulations. The IRB does not apply ICH Good Clinical Practice Guideline E6 to research. When the research is not federally funded or supported, nor subject to FDA oversight, the IRB may exercise judgement and flexibility as to whether and how the criteria set forth are required and/or applied.

1.7 Federalwide Assurance (FWA)

The HRPP operates under the authority of a current Federalwide Assurance (FWA00004706) and has designated two IRBs (IRB A registered as HHS IRB Registration# IRB00000703, IRB B registered as HHS IRB Registration #IRB00009717) to review all human research protocols. An Executive Management Team member is the signatory of and assumes the obligations of the FWA.

1.8 Research Covered by the HRPP

The HRPP covers all research involving human subjects that is under the auspices of Connecticut Children's. The research may be externally funded, funded from Connecticut Children's sources, or conducted without direct funding.

"Research under the auspices of Connecticut Children's" includes:

- 1) Research conducted at this institution;
- 2) Conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities;
- 3) Conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution; or
- 4) Involving the use of this institution's non-public information to identify or contact human subjects.

"Employees or agents" include individuals who:

- (1) Act on behalf of the institution;
- (2) Exercise institutional authority or responsibility; or
- (3) Perform institutionally designated activities.

"Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

Consistent with OHRP guidance, an institution is generally considered "engaged" in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

Examples of when Connecticut Children's would typically be considered "engaged in research" include the following:

- A Connecticut Children's employee or staff member conducts research at another healthcare facility, school, day care center, company, or community center in connection with his or her institutional responsibilities at Connecticut Children's.
- Connecticut Children's receives a direct award (through a grant, contract, or cooperative agreement) through HHS to conduct human subjects' research, even if all activities with human subjects are carried out by employees or agents of another institution;
- Connecticut Children's employees or agents interact with living individuals for research purposes; or intervene with living individuals by performing invasive or non-invasive procedures for research purposes, or by manipulating the environment;
- Connecticut Children's employees or agents obtain the informed consent of human subjects for research;
- Connecticut Children's employees or agents obtain, receive, or possess for research purposes identifiable private information or identifiable biological specimens from any source for the research;
- Connecticut Children's employees or agents release individually identifiable private information, or permit investigators to obtain individually identifiable private information, without the subjects' explicit written permission;
- Connecticut Children's employees or agents obtain, receive, or possess private information that is individually identifiable for the purposes of maintaining statistical centers for multi-site collaborative research;
- Connecticut Children's employees or agents maintain operations centers or coordinating centers for multi-site collaborative research.

NOTE: There may be limited exceptions to the examples outlined above. In some cases, the determination of engagement depends on the specific facts of a research study and may be complex. When research-related activities (including interacting with or gathering private information regarding Connecticut Children's patients) are conducted by persons who are not Connecticut Children's employees or agents, the IRB should be contacted. The IRB will make a case-by-case determination regarding whether the activities constitute engagement in research. The IRB will follow OHRP guidance when evaluating and making determinations regarding engagement in research. The relevant guidance is located at: <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-engagement-of-institutions/index.html>

1.9 Written policies and procedures

This manual, "Connecticut Children's Human Research Protection Program Standard Operating Policies and Procedures," details the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the IRB. This is not a static document. The policies and procedures are annually reviewed and revised as needed by the HRPP Director, HRPP Medical

Director, IRB Manager(s), and/or the Institutional Review Board. The Institutional Official will be informed of all substantive revisions to the policies and procedures.

The HRPP Medical Director and HRPP Director will keep the Connecticut Children's research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through electronic mailing lists. The policies and procedures will be available on the HRPP/IRB website and copies will be available upon request.

1.10 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. It consists of various individuals and committees such as: the Institutional Official, the Medical Director and Director of the HRPP, the IRB, IRB staff, other committees or entities addressing human subjects protection (e.g., Corporate Compliance/Conflict of Interest Committee, Scientific Review Committee, Research Compliance, etc.), investigators, research staff, and research pharmacy staff. The objective of this system is to assist the institution in fostering an ethical culture in the research enterprise, and ensuring that the institution meets ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for implementing the HRPP.

1.10.1 Institutional Official

The ultimate responsibility of the HRPP resides with the Institutional Official (IO), who is currently the Physician-in-Chief. The IO is responsible for ensuring the HRPP has the resources and support necessary to comply with all institutional policies and with federal regulations and guidelines that govern human subjects' research.

The IO also holds ultimate responsibility for oversight of the Institutional Review Board (IRB) and all Connecticut Children's investigators; for assuring the IRB members and investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and for the development and implementation of an educational plan for IRB members, staff and investigators. The responsibility for the HRPP is delegated by the IO to the Medical Director and Director of the HRPP.

1.10.2 Medical Director of the HRPP

The Medical Director of the HRPP (Medical Director) is a member of the medical faculty/medical staff, and has extensive knowledge and experience in the area of

human subjects' protection. The Medical Director reports updates to the IO and works closely with the HRPP Director, and is responsible for assisting with implementation of the HRPP, including:

1. Reviewing and approving new policies and procedures developed at Connecticut Children's (including revisions to existing policies and procedures) that have the potential to affect human subjects (e.g., HRPP, Clinical Trials, Office for Sponsored Programs, Pharmacy, etc.);
2. Reviewing findings from the HRPP Office quality assurance and quality improvement activities and compliance post-approval monitoring activities for research involving human subjects, and working closely with the IRB Chair and the HRPP Director as needed to implement corrective action plans;
3. Making recommendations to the IO and HRPP Director for developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research;
4. Providing consultation and support to the IRB Chair, IRB Manager(s), and HRPP Director, as needed;
5. Ensuring that IRB approved protocols are conducted in accordance with approved procedures, and that periodic monitoring occurs;
6. Conduct and/or oversee the conduct of data and safety monitoring and adverse event reporting, and notify the IRB as needed as issues arise;
7. Overseeing activities relating to observation of informed consent processes, as appropriate;
8. Making recommendations regarding the development of education and training requirements for investigators, IRB members and research staff;
9. In conjunction with the HRPP Director, ensuring that requirements regarding reporting to federal agencies are satisfied, and serving as a primary contact at Connecticut Children's for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services (DHHS) and other federal regulatory agencies;
10. Serve as the Research Integrity Officer (in accordance with the Connecticut Children's Research Misconduct Policy, available on the Connecticut Children's intranet);
11. Conducting educational and faculty development seminars for investigators in research ethics;
12. Foster communication among the IRB, Office of Grants and Sponsored Programs, and other Connecticut Children's offices or committees as appropriate to enhance a cohesive approach to research involving human subjects;
13. Serving as a resource to investigators in their efforts to carry out Connecticut Children's research mission;
14. Acting as HRPP liaison to the IRB, serving as a voting member of the IRB, to assist with resolution of questions or problems that may arise
15. Ensuring quality assurance/quality improvement activities for the IRB and HRPP (see Section 1.13).

1.10.3 Director of the HRPP

The Director of the HRPP (Director) has extensive knowledge and experience in the area of human subjects' protection, and reports updates to the Institutional Official. He or she has regulatory or legal expertise interpreting laws and regulations involving human subjects' research, and advises the IRB, IO, and others as needed in ascertaining the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. The Director is responsible for:

1. Implementing the institution's HRPP policy, including developing, managing and evaluating policies and procedures that ensure compliance with all state and federal regulations governing human subjects research, and overseeing all aspects of the HRPP program;
2. Providing institution-wide guidance and recommendations regarding the evolving ethical and legal standards relating to human subjects research, as well as evolving trends (e.g., new case law, recent federal enforcement actions, changes in state law, etc.);
3. Advising the Institutional Official, Medical Director, and IRB Chair on key matters regarding research with human subjects at Connecticut Children's, and providing consultation and support as needed;
4. Reviewing and approving new policies and procedures developed at Connecticut Children's (including revisions to existing policies and procedures) that have the potential to affect human subjects;
5. Managing and providing oversight for the HRPP and IRB staff, including training;
6. Providing oversight and guidance for the operations of the IRB Office;
7. Managing the day-to-day finances and budget of the Connecticut Children's HRPP and IRB, including annually assessing and reporting to the IO the financial needs of the Connecticut Children's HRPP;
8. Developing educational standards in human subjects' protection as appropriate for investigators, IRB members and research staff, and ensuring that training is completed on a timely basis; as well as providing educational opportunities throughout the institution on specific topics related to human subjects' protection;
9. Managing the quality assurance and quality improvement of the HRPP to measure adherence with federal regulations and state law governing human subjects' research, AAHRPP accreditation standards and institutional policies and use the data to make improvements and monitor compliance on an ongoing basis.
10. Working closely with the Medical Director and/or IRB Chair as needed to assist with implementation of any corrective action plans deemed

- necessary in response to post-approval monitoring other issues that may arise;
11. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
 12. Serve as a resource to investigators in their efforts to carry out the Connecticut Children's research mission;
 13. In conjunction with the Medical Director, ensuring that requirements regarding reporting to federal agencies are satisfied, and serving as a primary contact at Connecticut Children's for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services (DHHS) and other federal regulatory agencies, including drafting correspondence in response to government queries;
 14. Submitting, implementing and maintaining an approved FWA through the IO and the DHHS OHRP;
 15. Serving as the HRPP/IRB representative on the Corporate Compliance/Conflict of Interest Committee, to act as liaison and facilitate communication between the Corporate Compliance/Conflict of Interest Committee, HRPP, and IRB;
 16. Fostering communication among the IRB, Office for Sponsored Programs, and other Connecticut Children's offices or committees as appropriate to enhance a cohesive approach to research involving human subjects;
 17. Overseeing process for maintaining accreditation of the HRPP through the Association for the Accreditation of Human Research Protection Programs, Inc. ("AAHRPP");
 18. The HRPP Director may also perform some duties of the IRB Manager(s) regarding day-to-day operations of the IRB, consistent with the needs of the program.

1.10.4 Institutional Review Board (IRB)

Connecticut Children's has two IRBs, appointed by the Institutional Official. The IRB prospectively reviews and makes decisions concerning all human research conducted at its facilities or by its employees or agents, or under its auspices. The IRB is responsible for the protection of rights and welfare of human research subjects at Connecticut Children's. It discharges this duty by complying with the requirements of the Common Rule; state regulations, the FWA; and institutional policies, as applicable. (See Section 2 for a detailed discussion of the IRB)

1.10.5 Legal Department

The HRPP relies on the Legal Department as needed for the interpretations and applications of Connecticut law and the laws of any other jurisdiction where research is conducted as they apply to human subjects' research. Legal opinion may be sought

from the Legal Department as issues arise in the context of a particular research proposal.

In addition, the HRPP relies on the Legal Department's office for the monitoring activities conducted by the Research Compliance Manager.

1.10.6 Division/Department Heads

Medical Division heads, Surgery Department heads, Nursing Department heads, or qualified delegates are responsible for ensuring that the Principal Investigator (PI) is qualified by training and experience to conduct the proposed research. In addition, division heads are responsible for ensuring that the PI has sufficient resources and facilities to conduct the proposed research.

PIs are expected to consult with their Division/Department head before submitting a proposal to the IRB for review. Division heads are responsible for assuring that investigators have the resources required to conduct the research in a way that will protect the right and welfare of participants. Such resources include but are not necessarily limited to personnel, space, equipment and time.

1.10.7 The Investigator

The investigator is the ultimate protector of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards and for developing a protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent (unless specifically waived by the IRB) and the investigator must establish and maintain an open line of communication with all research subjects within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete appropriate training and must obtain all required approvals prior to initiating research. The investigator is also responsible for ensuring that each research protocol maintains ongoing IRB approval while any research activities occur. When investigational drugs or devices are used, the investigator is responsible for providing written procedures for their storage, security, dispensing and disposal.

1.10.8 Other Related Units

1.10.8.1 Office for Sponsored Programs

The Director (or designee) of the Office for Sponsored Programs (OSP) will review all research agreements with industry, federal, foundation, or non-profit sponsors. This institutional review ensures that all terms are in compliance with institutional policies. The Chief Executive Officer, Chief Operating Officer, or General Counsel will have the authority to endorse research proposals and execute research agreements on behalf of the institution.

When the federal grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of Connecticut Children's, a subcontract is executed between Connecticut Children's and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval upon request. The subcontract will flow down to the collaborating institution only those requirements mandated by the prime sponsor. The collaborating institution must also ensure that key personnel involved in human subjects' research are in compliance with the collaborating institution's policies or NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to Connecticut Children's. (See Section 12 for a more detailed discussion of sponsored research).

1.10.8.2 Connecticut Children's Pharmacy

A Connecticut Children's Clinical Specialist in Pharmacy serves on the IRB. In addition, one or more pharmacists fulfill the role of Investigational Drug Pharmacist within the Pharmacy Department. The Investigational Drug Pharmacist receives a final copy of any approved protocols involving investigational products (drugs or biologics) as they become active and on an ongoing basis as updates become available, and assures that information about all investigational products (IP) used in clinical trials is shared with the Pharmacy Staff, as appropriate.

The Pharmacy is typically responsible for managing the procuring, storage, preparation, and dispensing of IP used in both inpatient and outpatient clinical trials. If the IP is a controlled substance, it is ordered/received and stored by the Pharmacy and re-issued in appropriate quantities to researchers pursuant to a study-specific and patient-specific medication order developed by the Investigational Drug Pharmacist in collaboration with the Investigator or Clinical Trials team. If the need arises, the manufacture/compounding of drug products not commercially available is coordinated by the Connecticut Children's Pharmacy with outside vendors.

The Pharmacy is available to provide guidance to investigators in relation to the management of investigational products. The Pharmacy is also available to provide information to individuals conducting HRPP/IRB monitoring activities.

1.10.8.3 Scientific Review Committee

The Scientific Review Committee (SRC) reviews proposed research for issues of study design and scientific merit. All proposals except the following must be reviewed by the SRC prior to IRB review:

- Industry sponsored or multi-centered studies where Connecticut Children's is a participating site, not the lead site.
- Federally funded or other grant-funded studies which have undergone scientific review during the grant review process.

In addition, the SRC in partnership with the IRB may determine that additional exceptions are warranted depending on the level of IRB review required (for example, studies qualifying for exemption) or the experience of the PI. While the majority of the studies that meet one of the exceptions above do not require SRC review, the IRB may request SRC review in some circumstances.

The SRC assists investigators in identifying issues regarding study methodology including study design, data collection and management and statistical analysis, and may recommend changes as appropriate. The SRC assists the IRB in its evaluation of research protocols, and conveys their recommendations to the IRB that the study is found to be methodologically sound and can reasonably be expected to answer the proposed question, or that the SRC has identified reservations regarding the scientific soundness. The recommendations of the SRC are advisory to the IRB. Investigators may choose to submit a study for IRB review after scientific review, regardless of the findings/recommendations of the SRC. The IRB will consider the comments of the SRC but will ultimately determine whether the human subjects' protection criteria for approval of research are met.

1.10.8.4 Clinical Research Feasibility Committee (CRFC)

The CRFC is comprised of a multidisciplinary group of research professionals who provide a resource assessment of each study requesting team member support from either the Department of Research Operations & Development or the Department of Clinical Trials. Prior to IRB review, the committee reviews the study protocol and information provided by the Principal Investigator, Study Coordinator and Research Pharmacist to assess study complexity, anticipated time and effort and ancillary teams needed to execute the study protocol. This process enables early identification of logistical challenges, planning for identified gaps in resources, and increases likelihood of study success.

1.10.9 Relationship between Components

The IRB functions independently of, but in coordination with, other institutional regulatory committees. The IRB, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected. The IRB has review jurisdiction over all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that has adopted the human subjects' regulations.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has been disapproved by the IRB.

1.11 HRPP Operations

1.11.1 HRPP Office

The HRPP Director has primary responsibility for the day-to-day management of the HRPP Office, and has expert knowledge in regulatory issues regarding human subjects' protection. The HRPP Director reports directly to an Executive Management Team role at the Institution. The Director also serves as the Human Protections Administrator and is the primary contact at Connecticut Children's for the Office for Human Research Protections, Department of Health and Human Services.

The Director of the HRPP has oversight of the operations of the IRB. This includes responding to faculty, student, and staff questions about human subjects' research as well as oversight of organizing and documenting the review process. The Director works closely with the HRPP Medical Director and Chair of the IRB in the development of policy and procedures and he or she may be a voting member of the IRB and serves as Vice Chair of the IRB.

Additionally, the office is staffed by a Sr. IRB Manager, an IRB Operations Manager, and IRB Coordinator/Analyst. The duties and responsibilities for all staff are described briefly below; more complete information is included in their respective job descriptions.

The HRPP office informs the research community about policy updates and resources available through email notifications, website updates, and division meetings.

1.11.2 Sr. IRB Manager

The Sr. IRB Manager is responsible for all aspects of the IRB throughout the review process of a research proposal involving human subjects. The Sr. IRB Manager serves as a team leader for IRB Coordinator/Analyst and the IRB Operations Manager and is responsible for overseeing IRB record retention, and the maintenance of complete IRB files for research protocols and IRB correspondence (including e-mails) in accordance with the record retention policy as described in Section 4.7 of this document. The Sr. IRB Manager performs continuous quality improvement activities including periodic internal/self-assessment audits of the IRB program. The Sr. IRB Manager conducts ceded reviews when the Institution relies on an external IRB and expedited reviews of protocols under the Connecticut Children's IRB purview. (The HRPP Director may also share some of the duties of the IRB Manager(s) to maximize the efficiency of the office).

1.11.3 IRB Coordinator/Analyst

The IRB Coordinator/Analyst is responsible for providing administrative and clerical support to the IRB Chair, IRB Manager(s), and HRPP leadership, and scheduling and coordinating all IRB functions. The IRB Coordinator/Analyst is responsible for screening incoming submissions for accuracy and completion, including but not limited to completion of application, conflict of interest disclosures and current CITI training, and provides feedback and assistance to investigators and research staff throughout the review process. The IRB Coordinator/Analyst is also responsible for maintaining complete IRB files for all research protocols and IRB correspondence (including e-mails), and record retention. The IRB Coordinator/Analyst manages and oversees the content and presentation of the electronic Daily Management System (DMS) and team huddles, in coordination with the IRB leadership.

1.11.4 IRB Operations Manager

The IRB Operations Manager is responsible for providing program management for the installation, maintenance, and ongoing support of the web-based IRB data system (IRBManager), including the infrastructure to support integration with other research administration processes and systems to better support the research review processes. The IRB Operations Manager also works closely with the HRPP Director, Sr. IRB Manager, and other HRPP staff as needed to support gathering and analysis of data to assist with HRPP/IRB quality assurance and quality improvement activities. The IRB Operations Manager is responsible for coordinating the convened committee meetings, including conducting pre-review for greater than minimal risk research requiring review by the convened IRB committee, reviewing non-substantive contingencies and prepares minutes from the convened meeting. In addition, the IRB Operations Manager conducts expedited reviews of protocols under the Connecticut Children's IRB purview.

1.11.5 Selection, Supervision and Evaluation of HRPP Supporting Staff

1.11.5.1 Selection Process:

HRPP and IRB staff are selected in accordance with applicable Connecticut Children's Human Resources job descriptions and policies and procedures. Individuals who are responsible for business development are prohibited from carrying out day-to-day operations of the review process.

1.11.5.2 Supervision:

The HRPP Director is responsible for the day-to-day management and supervision of the HRPP and IRB Office staff, in accordance with applicable Connecticut Children's Human Resources and institutional policies and procedures.

1.11.5.3 Evaluation:

All staff are evaluated and receive feedback annually in accordance with applicable Connecticut Children's Human Resource performance management policies and procedures. The HRPP Director is responsible for conducting evaluations of the Sr. IRB Manager. The IRB Manager is responsible for conducting evaluations of the IRB Operations Manager and IRB Coordinator/Analyst. Evaluation of the IRB Coordinator/Analyst, IRB Operations Manager, and Sr. IRB Manager include timeliness of processing protocol submissions and expedited reviews communication with IRB personnel/committee members, investigators and research personnel, preparedness and documentation for convened meetings, knowledge of Institutional policy, local laws, and regulations governing human subjects research, and effectiveness of system upgrades and maintenance, as applicable to each role. IRB Staff receive written feedback.

All of the IRB staff are evaluated on a periodic basis (typically annually) by IRB Chair and Vice Chair for quality improvement purposes and to provide feedback to the IRB Staff regarding preparedness and documentation of IRB meetings as well as communication with the staff and committee. In addition, the research community is asked to complete a survey annually regarding their experiences with the IRB process and IRB staff. The HRPP Director uses aggregate data from the evaluations to develop content for IRB Staff training.

The IRB Chair and Vice Chair are evaluated on a periodic basis (typically annually) by the IRB members and IRB staff for quality improvement purposes and to provide feedback to the Chair and Vice Chair regarding committee operations and changes they may want to implement as they lead the committee. Results from this survey will be provided to the Institutional Official.

1.12 HRPP Resources

The IRB/HRPP Offices are located at 10 Columbus Boulevard, Hartford, CT. The mailing address for the IRB/HRPP Offices is 282 Washington Street, Hartford, Connecticut 06106. They are equipped with all necessary office space, storage space and equipment to perform the functions required for the IRB and HRPP. Meeting space for monthly IRB meetings is available at the main hospital location at 282 W Washington Street, Hartford, Connecticut 06106, but the majority of meetings are held virtually. Complete protocol files will be accessible to IRB members during meetings.

The Institutional Official provides resources to the IRB and HRPP Offices, including adequate staffing to efficiently conduct IRB and HRPP functions, and adequate meeting and office space. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines, will be made available to the

IRB and HRPP staff. The adequacy of personnel and non-personnel resources of the HRPP program is assessed on an annual basis by the HRPP Director and is reviewed and approved by the IO, in conjunction with the annual budget review process.

1.13 Quality Improvement/Quality Assurance

Connecticut Children's research compliance program incorporates quality improvement and quality assurance procedures to assess investigator compliance with Federal, State and local law and Connecticut Children's policies and to assess IRB Internal Compliance.

1.13.1 Institutional Periodic ("Not for Cause") and Directed ("For Cause") Reviews

The HRPP and Corporate Compliance offices have the primary responsibility for post-approval study reviews including periodic ("not for cause") and directed ("for cause") compliance reviews of research approved by the IRB as described in Section 2.4.3.

Periodic compliance reviews are conducted by the Research Compliance Manager, who reports to the General Counsel, and works in collaboration with the HRPP Director and HRPP Medical Director. The Research Compliance Manager primarily conducts periodic compliance reviews of on-going clinical and translational research studies to evaluate and assess current practice and compliance with the IRB approved protocol and federal, state and local regulations. Studies are randomly selected for periodic compliance reviews based on the following criteria: level of risk to study subjects, study population and complexity of protocol, investigator-initiated studies, investigator held IND's or IDE's, studies conducted by investigators or research staff who are new to research and frequency of protocol deviations and/or adverse events.

Periodic compliance review activities include, but are not limited to the following:

- Assessment of the roles, responsibilities and training of research staff and corresponding documentation;
- Evaluation of documentation of informed consent, assent and HIPAA authorization;
- Observation of the consent process;
- Verification of subject eligibility;
- Regulatory and IRB documentation review;
- Assessment of subject recruitment process and compensation;
- Review of source documentation and adherence to protocol;
- Evaluation of study drug accountability (if applicable);
- Assessment of adverse event and unanticipated problem reporting;
- Assessment of research record confidentiality and data security.

Results from periodic compliance reviews are used to identify areas for improvement as well as suggest recommendations based on existing

policies and procedures. The HRPP Director and/or the HRPP Medical Director and the Research Compliance Manager also meet regularly to discuss review findings and develop educational activities designed to address common findings.

Directed reviews are initiated when there is a concern or an allegation of research activity that compromises subject safety or study integrity. Directed reviews are conducted by the Research Compliance Manager and are focused on the area of concern identified and may include all or some of the items reviewed during a periodic, not-for-cause compliance review. The cause of the compliance review may not be communicated to the research staff until after the review has been completed.

1.13.2 Non- Institutional Directed Reviews and Compliance Reviews

External directed (“for cause”) compliance reviews may be conducted at non-Connecticut Children’s sites, where the Connecticut Children’s IRB serves as the “IRB of Record,” to assess compliance with federal and state regulations, research subject safety, and IRB policies and procedures. These directed reviews are implemented in response to identified concerns that require an IRB determination.

1.13.3 Reporting and Disposition

The results of periodic reviews from the post-approval audits are reported to the Principal Investigator and associated research staff, the HRPP Medical Director, HRPP Director, and may be shared with IRB members when applicable. The findings for both “for cause” and “not for cause” reviews will also be shared with the IRB reviewers during continuing review. The Research Compliance Manager is responsible for evaluating findings and formulating corrective action plans as necessary, in collaboration with the HRPP Medical Director and HRPP Director.

The Research Compliance Manager conducting “for cause” or “not for cause” reviews will notify the HRPP Medical Director or the HRPP Director, as applicable, if subjects in a research project have been exposed to unexpected serious harm. Any non-compliance will be handled according the procedures in Section 9 of this Manual (Complaints and Non- Compliance).

1.13.4 Conduct of Quality Assurance/Quality Improvement Activities for IRB Operations (IRB Internal Compliance Reviews)

The overall objective of the HRPP Quality Assurance / Quality Improvement Plan is to measure and improve human research protection program effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

1.13.4.1 Quality Improvement Metric 1– Daily Management System (DMS)

On a weekly basis, the IRB team employs the lean strategy for continual improvement through a focused discussion of the Daily Management System (DMS) board. As part of these huddles, the IRB team reviews the following categories of activities:

- *Abnormality tracking*: the IRB team identifies, reviews, and addresses next steps for abnormalities in the following five categories according to MESS5S: methods, equipment, staff, supplies, and space. If there are areas that are identified as abnormalities repeatedly, systematic tracking of the abnormality takes place and then the group identifies and implements a corrective action.
- *Guidance*: The IRB team identifies additional guidance needed for the research community, schedules, and prioritizes the development of new resources.
- *Quick fixes and big issues*: The IRB team reviews the status of those items identified as “quick fixes” or “big issues.”
- *Idea improvement*: if the research community or team member propose an idea for improvement, the IRB team reviews the proposed idea and makes a plan for implementation if feasible.
- *Situational awareness*: the IRB team reviews any changes to upcoming team member schedules and institutional announcements.

1.13.4.2 Quality Improvement Metric 2 – IRB Meeting Minutes

Another goal of the quality improvement activities is to ensure that the meeting minutes include documentation that the reviews are conducted in accordance with the Federal, state and local regulations and institutional policy. The IRB internal compliance review will include, at a minimum, a review of the IRB meeting minutes to determine if the minutes include the following elements.

1. Names of members present including alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster)
2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. When members left and returned to the room
4. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
5. Vote on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those excused, Number of those recused)
6. An indication that, when an IRB member has a conflicting interest (see Section 2.3.2) with the research under review, the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained. When IRB Members recuse themselves from the final deliberation and vote on a research study due to a conflict, their names and the nature of their conflict is noted in the minutes and the reason for their departure is documented as a recusal due to a conflict of interest.

7. Approval period for initial and continuing approved protocols
8. Risk level of approved initial review protocols and continuing review protocols
9. When approving research that involves children (most of the research at Connecticut Children's), the IRB's justifications and findings regarding the determinations stated in the Subpart D or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.
10. The basis for requiring changes in or disapproving research

If less than 90% of the above-cited items are included in the IRB minutes, the HRPP Director and the HRPP Medical Director will develop a corrective action plan which may include: IRB staff training; an independent audit of the IRB operations; and IRB member training regarding the Federal, State and local regulations and Connecticut Children's policies regarding full Board review of research involving human participants.

1.13.4.3 Additional IRB Internal Compliance Reviews

The Quality Assurance / Quality Improvement Plan may also include additional internal directed audits and random internal compliance reviews implemented by the HRPP Director. The HRPP Director may designate appropriate HRPP staff members to conduct such reviews, or may request external assistance where appropriate

Activities may include but not be limited to the following:

- a) Assess the current adverse event reporting process;
- b) Assess that privacy provisions, according to HIPAA, have been adequately reviewed;
- c) Assess and maintain the accuracy of the electronic IRB application and related documents;
- d) Assess the adequacy of annual education and training requirements for investigators and staff;
- e) Evaluate the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review (or that if a lapse occurred, no research activities took place);
- f) Observe IRB meetings or other related activities;
- g) Review IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- h) Review the IRB database to assure all fields are completed accurately;
- i) Review of evaluations by the IRB members;
- j) Verification of IRB approvals for collaborating institutions or external performance sites;
- k) Periodically solicit feedback from investigators and others in the research community
- l) Other monitoring or auditing activities deemed appropriate by the IRB and HRPP.

1.13.4.4 Metrics

As a way of promoting transparency to the research community and to evaluate against internal and external benchmarks, IRB staff review and share IRB review times. Connecticut Children's measures the following IRB review times:

- Time from submission to review by the convened IRB;
- Time from submission to approval by the convened IRB;
- Time from submission to approval by expedited procedure;
- Time from submission to an exempt determination

If the Connecticut Children's IRB review times are significantly greater than the IRB review times reported by AAHRPP, the HRPP Director and the HRPP Medical Director will develop a corrective action plan which may include: IRB staff training; an independent audit of the IRB operations; and PI and study coordinator training on the process for responding to IRB contingencies.

1.13.4.5 Reports and Disposition

The HRPP Director will review the results of internal IRB compliance reviews with the HRPP Medical Director and IRB Chair. If any deficiencies are noted in the review, a corrective action plan will be developed by the HRPP Director and Medical Director and approved by the Institutional Official. The HRPP Director will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the Institutional Official. Reports of the results of quality assurance/quality improvement activities may impact current practices and may require additional educational activities. Reports will be made periodically to the IO as needed.

1.13.5 Additional Quality Improvement Activities

Study Initiation Meetings:

The Research Compliance Manager conducts study initiation meetings with principal investigators and associated research staff to ensure the following:

- correct understanding of the study protocol, study procedures, study start-up materials, and roles and responsibilities of each staff member
- identify regulations and policies pertinent to the study
- provide material and tools to facilitate adherence for each new study (e.g. regulatory binders with labeled tabs)

Ongoing Research Education

The HRPP (in particular the IRB staff, Research Compliance Manager, and representatives from the Office of Grants and Sponsored Programs) are committed to helping investigators and research staff navigate federal and state research regulations, guidance, and organizational policies through various forums including but not limited to:

- New Investigator/Research Staff Training Sessions

- Small group sessions
- Research Education Series presentations
- Information distributed through emails, the HRPP Newsletter and OGSP Newsletter
- Tailored education as a result of findings from study reviews

1.14 Collaborative Research Projects

Background

Relevant guidance from OHRP states that multiple institutions engaged in the same non-exempt human participant research may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort. Similarly, FDA regulations permit a sponsor to utilize a single, central IRB for review of multicenter clinical trials.

The purpose of this policy is to define the procedures and standards the Connecticut Children's Medical Center Human Research Protection Program follows for determining when to accept the review of another IRB for non-exempt human-participant research in which Connecticut Children's and employees/agents are engaged, and when to permit another institution or an unaffiliated researcher to rely upon the review of a non-exempt human-participant protocol by the Connecticut Children's IRB. Presently, Connecticut Children's can only enter into reliance agreements with other U.S. domestic Institutions.

Policy Statement

When non-exempt human participant research is being conducted in collaboration with other institutions or with collaborating individual investigators, each collaborating institution and/or collaborating individual investigator engaged in the research must obtain IRB approval from an appropriately authorized IRB. The OHRP guidance document, *Guidance on Engagement of Institutions in Human Subjects Research* will be used as the basis for determining whether the duties contemplated by an investigator constitute engagement in human participant research. Such determinations will be made in collaboration and consultation with authorized representatives of the collaborating institution and/or the collaborating individual investigators, as applicable.

In an effort to streamline IRB reviews for multicenter trials, Connecticut Children's HRPP will consider requests to either rely on another institution's IRB or to serve as the Reviewing IRB for other collaborating sites engaged in the trial under the conditions set forth in this policy. The Signatory Official or delegate, in consultation with the Legal Department and HRPP representatives, has the authority to execute Institutional Authorization Agreements (IAAs) or Reliance Agreements (RAs) on behalf of the Connecticut Children's. All determinations to rely upon, or to permit another institution to rely upon the Connecticut Children's IRB, shall be documented in an IAA or RA. The IAA or RA documents the roles of the Reviewing IRB and the relying organization(s).

Connecticut Children's is a SMART IRB Participating site, and preferably utilizes the SMART IRB Master Reliance Agreement for reliance scenarios, with acknowledgement/documentation of ceded review on a study-by-study basis. When the SMART IRB Master Reliance Agreement is not utilized, applicable terms of the agreement will be negotiated on a case-by-case basis in consultation with the HRPP Directors and the Legal Department. Participating Institutions may also rely on one another under this Agreement for determinations and documentation of exemption.

The research community is provided with information on the process to utilize Connecticut Children's as the reviewing IRB and to rely on an external IRB through ongoing education, individual/group training, the HRPP SOPs, and job aids/guidance/tools that are made available through the HRPP internal website and periodic announcements.

1.15 IRB RELIANCE MECHANISMS

1.15.1 Connecticut Children's IRB Reliance on an External IRB

Investigators considering requesting reliance on another IRB should contact the IRB office early in the research proposal process. Decisions about whether to permit reliance on another IRB shall be determined by the Sr. IRB Manager, in consultation with the Director(s) of the HRPP. Connecticut Children's may rely on another appropriately constituted IRB for the review of cooperative research projects under the conditions set forth below.

In deciding whether or not to rely on an external IRB, the Sr. IRB Manager will consider the following criteria:

- Whether the use of a Central IRB mechanism has been mandated by the study sponsor or research consortium.
- Whether the study is federally supported and falls under the NIH's sIRB mandate.
- The anticipated level of risk associated with proposed studies.
- The terms and conditions of the proposed IA or RA.
- Whether the reviewing IRB's policies and procedures meet Connecticut Children's standards, as determined by the HRPP Director or designee. If the other IRB is AAHRPP accredited, then it will be presumed that the Connecticut Children's standards are being met; however, accredited status does not in itself necessarily suffice as a basis for the reliance decision.
- Whether the reviewing IRB has particular expertise for reviewing the research
- The location where the interventional human research activities will take place.
- The capacity of the other institution and its IRB to sufficiently be informed about the Connecticut Children's local research context and applicable laws and regulations.
- Whether the reviewing IRB will be serving as the HIPAA Privacy Board.

Commercial IRBs are independent pay-for-service IRBs that provide regulatory and

ethical review services of research involving human subjects. There are additional considerations for Industry sponsored protocols whereas reliance on a Commercial IRB has been requested:

- Sponsor must require that all participating sites utilize the Commercial IRB for the regulatory review of the study.
- Sponsor must agree to pay for all fees imposed by the Commercial IRB, including site specific fees charged by the Commercial IRB such as a change in the local PI or local consent form.
- Sponsor must agree to pay for Connecticut Children's IRB review fees for the review of local context requirements including State/local law and Institutional Requirements, ancillary reviews, Resources, Conflict of Interest, Training/qualifications, and HIPAA privacy review (when applicable).
- Commercial IRB is AAHRPP-accredited.
- Commercial IRB must be a SMART IRB participating site and agree to utilize the SMART IRB Master Reliance Agreement as the basis for the ceded review/reliance relationship.

In order to initiate discussions with the Reviewing IRB, the Connecticut Children's investigator must provide the Connecticut Children's IRB with: 1) contact information for the Reviewing IRB, 2) a draft version of the agreement, 3) a copy of the local context form, and 4) standard operating procedures if the Institution/Reviewing IRB is not AAHRPP accredited.

Connecticut Children's will rely upon AAHRPP-accredited IRBs or ECs, except when this is not possible. For minimal risk research, Connecticut Children's IRB may simply 1) Obtain an assurance from the non-accredited IRB or Ethics Committee (EC) that it will conduct its review consistent with the applicable ethical standards and regulations, and that it will report any regulatory violations or investigations of the reviewing IRB or EC by regulatory agencies, such as OHRP or the FDA; and 2) Request the reviewing IRB or EC to attest that it has completed its own internal quality review process, such as use of AAHRPP's Evaluation Instrument for Accreditation to conduct a self-assessment, completion of the US FDA's self-evaluation checklist for IRBs or ECs, or another process satisfactory to the relying organization.

In order to maintain an accurate record of studies being done at the institution, as well as to manage required ancillary reviews, consider any relevant laws, regulations or policies applicable to protection of human participants, and assess whether local context language has been appropriately included within Consent/HIPAA documents, investigators are required to submit an abbreviated Application for Research on Human Subjects in

IRBManager, requesting reliance on the external IRB. The Sr. IRB Manager, or delegate, will provide a local approval letter once the study has met all Institutional Requirements, which in essence is documentation to acknowledge receipt of the information and activate the study to begin at Connecticut Children's.

An appropriately executed IRB Authorization or Reliance Agreement must be in place, preferably with other SMART IRB participating site, utilizing the SMART IRB Master Reliance Agreement. All finalized agreements will be maintained within Contract Guardian, as well as within the IRB/HRPP electronic files.

Modifications to the IRBManager application are required for:

- 1) Study-wide amendments that result in changes to IRB Determinations made by the Reviewing IRB or newly approved Protocol documents/Consent/HIPAA forms.
- 2) Local amendments, including protocol changes that may trigger local ancillary review or study personnel changes so that the Connecticut Children's IRB can verify training requirements and ensure any relevant COI management plans are communicated to the Reviewing IRB.

In addition, a continuation/progress report is required for studies that required continuing review as determined by the Reviewing IRB. Information reported should be only that for the local site, and include the Reviewing IRB continuation approval letter and any newly stamped/approved participant facing materials such as consent/assents forms. Connecticut Children's IRB is responsible for maintaining and updating local considerations/context for it's site when applicable to the study. Study closures should also be reported to Connecticut Children's using the continuation/closure form in IRBManager.

Lastly, Reviewing IRB Determinations of serious or continuing Non-Compliance and Unanticipated Problems that are related to Connecticut Children's researchers and participants, and study suspensions or terminations should be submitted to Connecticut Children's IRB through the Reportable New Information mechanism in IRBManager.

1.15.2 Another Institution's Reliance on the Connecticut Children's IRB

The Connecticut Children's IRB may serve as the Reviewing IRB for another institution with appropriately executed IRB Authorization or Reliance Agreements, preferably with other SMART IRB participating sites, utilizing the SMART IRB Master Reliance Agreement. When utilizing the SMART IRB Master Reliance, Connecticut Children's requires the Relying site to document reliance utilizing the Institution's Smart IRB Acceptance and Flexibility Acknowledgement, which clarifies the terms of the SMART IRB Agreement that were intentionally designed to be flexible to accommodate the needs of

Reviewing IRBs and Relying Institutions for Research under Ceded Review.

In deciding whether to provide IRB review for another institution, the Sr. IRB Manager may consult with the Director(s) of the HRPP, and make a determination based on the following criteria:

- The subject matter and whether the Connecticut Children's IRB has the expertise for reviewing the study.
research The number of sites engaged in the research.
- The risk level of the study.
- Whether the study is being conducted under an investigator-initiated IND or IDE.
- The location where the interventional human research activities will take place.
- Whether the study is federally supported and falls under the NIH's sIRB mandate.
- Whether the use of a Central IRB has been mandated by the sponsor or research consortium.
- The Connecticut Children's capacity to be sufficiently informed about the particular characteristics of the other institution's local research context and local applicable laws and rules.
- Whether Connecticut Children's IRB will serve as the HIPAA Privacy Board.

In order to initiate discussions with the institution requesting to cede IRB Review, the Connecticut Children's investigator must 1) have the study approved by the Connecticut Children's IRB, 2) contact information for the collaborating institutions' IRBs; and 3) a copy of the approved protocol and if applicable, a consent template document which indicates areas where the Relying Institutions must add information.

The Legal Department will work in drafting an appropriate form of RA which will be provided to the IRB representatives at each collaborating institution for review and comment. All comments will be considered and a final version of the agreement will be forwarded for signature along with a local context form. All finalized agreements will be maintained within Contract Guardian, as well as within the IRB/HRPP electronic files.

The Connecticut Children's investigator is required to create an Application for Research on Human Subjects in IRBManager, and obtain review and approval by the Connecticut Children's IRB. Upon approval, the Sr. IRB Manager or delegate, will provide the Connecticut Children's investigator with 1) the finalized protocol and applicable attachments, 2) the consent template with unlocked fields for local language to be inserted, and 3) the IRB approval letter.

Requests to add study sites will be reviewed as a minor change to the study using an expedited review procedure, provided the site will be following the same protocol that has already been reviewed and approved, and that there is no overall increase to study-wide enrollment. If there is an increase to overall study-wide enrollment, the modification will be reviewed by the convened committee for studies that were determined to be greater than minimal risk.

The Connecticut Children's Investigator is responsible for all submissions to the

Connecticut Children's IRB through IRBManager, including modifications, continuations, reports of potential serious or continuing non-compliance and unanticipated problems. Relying organizations should relay any pertinent information for their site directly to the Connecticut Children's Investigator, who will in turn communicate the information to the Connecticut Children's IRB through a submission in IRBManager.

Primarily, the Connecticut Children's Investigator, in consultation with the Sr. IRB Manager, will facilitate communication with the relying institution about IRB actions on the human subject research that is the subject of the Agreement, in accordance with its specific provisions of the Reliance Agreement. This includes the provisions in place for the management of information provided to and obtained from the relying sites, such methods of managing information that is relevant to the protection of participants, including reports of potential serious or continuing non-compliance and unanticipated problems and the final determination by the Connecticut Children's IRB. The Connecticut Children's Investigator is also responsible for relaying any outcomes related to study suspensions, terminations, or study closures. The Relying Site is responsible for maintaining and updating local considerations/context for its site when applicable to the study, and communicating any changes to the Connecticut Children's Investigator and IRB.

The Relying Organization may communicate directly with the IRB when necessary to discuss questions, concerns, or obtain interpretation of IRB determinations.

1.15.3 Serving as IRB of Record for an Entity Without an IRB

The Connecticut Children's IRB may serve as the IRB of record for an entity that does not have its own IRB if (a) Connecticut Children's is directly involved in the conduct of or funding of the human subjects research at the entity; (b) the HRPP Director or designee approves of the arrangement in advance; c) there are no unresolved conflict of interest issues; (d) the scope of the reliance is limited to the human subject research project in which Connecticut Children's is directly involved, and (e) the entity enters into an appropriate form of an agreement with Connecticut Children's. Agreements will be maintained within Contract Guardian, as well as within the IRB/HRPP electronic files.

1.15.4 Serving as IRB of Record for a Non-Affiliated Individual Investigator

When a non-affiliated individual investigator is engaged in human participant research, Connecticut Children's IRB may choose to extend its FWA to cover that individual's activities provided that Connecticut Children's is otherwise engaged in the human subject research. In such cases, an Individual Investigator Agreement (IIA) outlining the terms and conditions of this arrangement must be executed by the HRPP Director or designee, as well as the individual investigator. The executed IAAs will be maintained within Contract Guardian, as well as within the IRB/HRPP electronic files.

1.15.5 Research Reviewed by the National Cancer Institute (NCI) Pediatric Central IRB (CIRB)

Connecticut Children's has had a long-standing Master Reliance Agreement with the National Cancer Institute Central IRB, where the Pediatric CIRB has served as the Reviewing IRB for COG clinical trials taking place at Connecticut Children's. The Master Reliance agreement will be maintained within Contract Guardian, as well as within the IRB/HRPP electronic files.

The Connecticut Children's IRB requires the local Investigator to submit an abbreviated Application for Research on Human Subjects in IRBManager, requesting reliance on the external IRB. The Sr. IRB Manager, or delegate, will provide a local approval letter once the study has met all Institutional Requirements, which in essence is documentation to acknowledge receipt of the information and activate the study to begin at Connecticut Children's. Modifications to the IRBManager application are only required for:

- 1) Study-wide amendments that result in changes to the Connecticut Children's HIPAA forms, which remain under the purview of the Connecticut Children's IRB.
- 2) Local amendments, including protocol changes that may trigger local ancillary review or study personnel changes so that the Connecticut Children's IRB can verify training requirements and ensure any relevant COI management plans are communicated to the Reviewing IRB.

The Investigator is not required to include supporting documents, such as the protocol document and consent forms, at the time of any NCI CIRB reliance submission. The investigator is responsible for ensuring that the consent form has been edited so that it complies with Connecticut Children's boilerplate language institutional requirements.

In addition, a continuation/progress report is required for studies that require continuing review as determined by the NCI CIRB. Information reported should be only that for the local site. Study closures should also be reported to Connecticut Children's using the continuation/closure form in IRBManager. Lastly, NCI CIRB Determinations of serious or continuing Non-Compliance and Unanticipated Problems that are related to Connecticut Children's researchers and participants, and study suspensions or terminations should be submitted to Connecticut Children's IRB through the Reportable New Information mechanism in IRBManager.

1.15.6 Collaborative Research at both Connecticut Children's and a Neighboring Institution

The Connecticut Children's IRB has had a long-standing Cooperative Agreement with four neighboring Institutions, Hartford HealthCare, The Jackson Laboratories, The University of Connecticut Health Center, and the University of Connecticut (Storrs campus), which in essence operates similarly to a Master Reliance Agreement. Many studies have been included under this agreement which has reduced the burden on the local investigators.

If the Connecticut Children's IRB is to be the Reviewing IRB, the Connecticut Children's investigator submits the study (or amendment to add the neighboring Institution as a relying site) to the Connecticut Children's IRB through IRBManager, and indicates in the

application that this is a multi-center study for which Connecticut Children's will serve as the reviewing IRB for one or more other institutions. Any study-specific research personnel from the neighboring Institution should be included in the Connecticut Children's IRB application study personnel table to verify training, annual disclosure requirements, and qualifications have been met, with the exception of research collaborators from The Jackson Laboratories. In lieu of including The Jackson Laboratories investigators on the Connecticut Children's IRB application personnel table, The Jackson Laboratories IRB independently confirms training requirements and qualifications of their personnel, and provides any conflict of interest management plans to the Connecticut Children's IRB.

If the Connecticut Children's IRB agrees to serve as the Reviewing IRB, the IRB outcome letter will indicate such, and the neighboring IRB is cc'd on the communication. The research team is responsible for then submitting an abbreviated application through the neighboring IRB requesting reliance on Connecticut Children's IRB, and in turn, the neighboring IRB will invoke the Cooperative Agreement for the specific study, and provide directly to the Investigator and Connecticut Children's IRB for documentation of reliance.

For scenarios where a University of Connecticut (Storrs campus) student is research personnel on a study conducted at Connecticut Children's, without the research being modified for the purposes of the student (e.g., additional survey questions, additional experiments, additional or modified aims/objectives), the student is not acting as an agent of the University of Connecticut. This is true even when the experience will result in course credit or otherwise count towards the student's degree progression. In these scenarios, reliance is not necessary per University of Connecticut (Storrs campus) policy.

A virtually identical process applies when a researcher at Connecticut Children's requests to cede review to a neighboring Institution. Generally, researchers are exempt from duplicative ongoing reporting of amendments, continuations, and study closures. In lieu, the Reviewing IRB provides outcome letters for such events. However, reports of serious or continuing non-compliance and unanticipated problems that are related to Connecticut Children's researchers and participants, and study suspensions or terminations should be submitted to Connecticut Children's IRB through the Reportable New Information mechanism in IRBManager, even when Connecticut Children's cedes review to the neighboring Institution's IRB.

2 Institutional Review Board

2.1 Policy

Connecticut Children's has established Institutional Review Boards (IRB) to ensure the protection of human subjects in human subjects research conducted under the

auspices of Connecticut Children's. All non-exempt human subjects research conducted under the auspices of Connecticut Children's must be reviewed and approved by the Connecticut Children's IRB prior to the initiation of the research.

The following describes the authority, role and procedures of the Connecticut Children's.

2.2 IRB Authority

Per Connecticut Children's organizational policy, "Human Research Subjects Protection Program (HRPP)", the IRB is authorized:

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of Connecticut Children's;
2. To suspend or terminate approval of research not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to participants or others;
3. To observe, or have a third party observe, the consent process; and
4. To observe, or have a third party observe, the conduct of the research.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has been disapproved by the IRB. Connecticut Children's officials may strengthen requirements and/or conditions, or add other modifications to secure Connecticut Children's approval or approval by another Connecticut Children's committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications. The IRB Chair makes the determination of whether the changes require full IRB re-review or expedited review.

2.3 Number of IRBs

There are currently two institution-wide IRBs. The IO will consult with HRPP leadership on an annual basis to make a determination as to the appropriate number of IRBs that are needed for the institution. This determination will be based on the evaluation of the performance of the IRB as described in Section 1.13.4.

2.4 Roles and Responsibilities

2.4.1 Chairperson of the IRB

The Institutional Official, in consultation with the HRPP Director, Medical Director, and as necessary, IRB members, appoints a Chair and Vice-Chair of the IRB to serve for renewable three-year terms. Any change in appointment, including reappointment or

removal, requires written notification.

The IRB Chair should be a highly respected individual from within Connecticut Children's, preferably a faculty member of senior rank, fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by the institution's administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources.

The IRB Chair is responsible for conducting the meetings and is a signatory, when needed, for correspondence generated by the IRB.

The IRB Chair may designate other IRB members (e.g., the Vice Chair or HRPP Director) to perform duties, as appropriate, for review, signature authority, and other IRB functions.

The IRB Chair advises the HRPP Director and Institutional Official about IRB member performance and competence.

The performance of the IRB Chair will be reviewed and receive feedback on an annual basis by the HRPP Director in consultation with the Institutional Official, as part of the annual assessment of IRB/HRPP resources and needs. If the Chair is not acting in accordance with the IRB's mission, is not following these policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she may receive additional training and may be removed.

2.4.2 Vice Chair of the IRB

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and has the same, authority, and duties as Chair. The performance of the IRB Vice Chair will be reviewed and receive feedback on an annual basis by the IRB Chair.

2.4.3 Subcommittees of the IRB

The Chair, in consultation with the HRPP Director, may designate one or more other IRB members, i.e. a subcommittee, to perform duties, as appropriate, for review, signature authority, and other IRB functions.

Duties of a subcommittee may include the following:

1. Serve as designees by the IRB Chair for the **expedited review** of new or continuing protocols, and/or modifications of continuing protocols. The subcommittee should be experienced in terms of seniority on the IRB, and must be matched as closely as possible with their field of expertise to the study, and must be trained on the expedited review process.

2. **Review and approve the revisions requiring only simple concurrence** submitted by investigators for a protocol given provisional approval, i.e. “Contingent Approval Pending Minor Clarifications”, by the convened IRB.
3. **Conduct an inquiry.** A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to conduct an inquiry into allegations of non-compliance. The subcommittee is given a charge by the IRB, which can include any or all of the following:
 - a. Review of protocol(s) in question;
 - b. Review of FDA (or other internal or external) audit report of the investigator, if appropriate;
 - c. Review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human subjects;
 - d. Interview of appropriate personnel if necessary;
 - e. Preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting;
 - f. Recommend actions if appropriate.
4. **Conduct on-site review.** Determination of the review interval and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by an IRB subcommittee might occur or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

2.5 IRB Membership

IRB members are selected based on appropriate expertise, diversity (including consideration of race, gender, cultural backgrounds, and specific community concerns in addition to representation by multiple, diverse professions), and knowledge and experience with vulnerable subjects (particularly children). Membership will include both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at Connecticut Children's. Connecticut Children's has procedures that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise (See Section 3.6.3).

In addition, the IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in Connecticut Children's research (e.g., children).

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary

to review specific research activities. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals who are responsible for business development are prohibited from serving as members on the IRB.

2.6 Composition of the IRB

1. The IRB shall have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
2. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
3. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional policies, resources and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.
4. If the IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these categories of subjects. When protocols involve these categories of subjects, the review process shall include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the IRB or as consultants.
6. The IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
7. The IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
8. The IRB shall have at least one member who represents the perspective of research participants.
9. One member may satisfy more than one membership category.
10. The HRPP Director, Medical Director, and any other appropriate administrators of

the HRPP Office may be voting members of the IRB.

2.7 Appointment of Members to the IRB

The IRB Chair, Medical Director, or HRPP Director may identify a need for a new or replacement member, or alternate member. The IRB Chair, Medical Director, and HRPP Director propose candidates who have the expertise needed by the IRB and who are willing to serve. Others may also suggest names of persons willing to serve.

The final decision in selecting a new member is made by the Institutional Official, the IRB Chair, and the Director of the HRPP Office. Appointments are made by the Institutional Official and are for a renewable three-year period of service. Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written notification to the Chair.

On a periodic basis the IRB Chair and the Director of the HRPP Office review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

2.8 Alternate members

The appointment and function of alternate members is the same as that for primary IRB members, and the alternate's expertise and perspective are comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member shall receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) for whom each alternate member may substitute. The alternate member shall not be counted as a voting member unless the primary member is absent. The IRB minutes shall document when an alternate member replaces a primary member.

2.9 IRB Member Conflict of Interest

No regular, alternate, or ex officio member may participate in the review (initial, continuing, modification, unanticipated problem involving risk to subjects or others, or non-compliance with regulations or laws or the requirements of the IRB) of any research project in which the member has a conflict of interest (COI), except to provide information as requested. This conflict of interest policy applies to both expedited and full Board reviews. It is the responsibility of each IRB member to disclose any COI in a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room. Each IRB member is expected to submit his/her interests via the

annual disclosure process.

Committee members may find themselves in any of the following conflicts of interest when reviewing research:

1. The member or consultant has a significant role in the design, conduct, or reporting of the research.
2. An immediate family member of the member or consultant is involved in the design, conduct, or reporting of the research. Immediate family member is defined as spouse or domestic partner and dependent children.
3. The member holds significant financial interests in the sponsor of the research or significant financial interest in the research being reviewed (See Section 13 for a definition of significant financial interests).
4. The member is an executive or director of the agency or company sponsoring the research
5. The member has an interest that the member believes conflicts with his or her ability to objectively review a protocol.

The IRB Chair will poll IRB members at each convened meeting to determine if a COI exists regarding any protocols to be considered during the meeting and reminds them that they should recuse themselves by leaving the room during the discussion and vote of the specific protocol. If a member responds affirmatively to the existence of a potential conflict, the Chair will ensure that the member does not participate in the final deliberations and vote. IRB members with a conflicting interest are excluded from being counted towards quorum. All recusals by members with COI are recorded in the minutes.

If the Conflict of Interest status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair and/or Manager of the IRB Office.

2.10 Use of Consultants

When necessary, the HRPP Director, the IRB Chair, Vice-Chair, or IRB Manager(s) may solicit individuals from Connecticut Children's or the community with competence in special areas to assist in the review of issues or protocols, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB. The need for an outside reviewer is determined in advance of the meeting by the HRPP Director, the IRB Manager(s), or the Chair or Vice-Chair by reviewing the protocols scheduled to be reviewed at the convened meeting. The IRB Manager will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Written statements of consultants will be kept in IRB records. Key information provided

by consultants at meetings will be documented in the minutes. Written reviews provided by the outside reviewer will be filed with the protocol.

The IRB Chair, Vice-Chair, or IRB Manager(s) reviews the conflict of interest policy for IRB members with consultants. Consultants must verbally confirm that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or family members have a conflicting interest in the sponsor of the research will not be invited to provide consultation.

The consultant's findings will be presented to the full board for consideration either in person or in writing. If in attendance, these individuals will provide consultation but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

2.11 Duties of IRB Members

The agenda, submission materials, protocols, proposed informed consent forms and other appropriate documents are distributed to members at least one week prior to the convened meetings at which the research is scheduled to be discussed. There are no pre-specified limits on the number of items on the agenda. However, IRB staff takes into account Board member availability, expertise, and agenda length. Members review the materials before each meeting, in order to participate fully in the review of each proposed project. IRB members will treat the research proposals, protocols, and supporting data confidentially. Any paper copies of the protocols and supporting data are deposited at the conclusion of the review for professional document destruction (with the exception that protocols requiring further review may be retained by IRB members as needed for reference purposes for future convened meetings).

2.12 Attendance Requirements

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or the IRB Manager(s). If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the Chair, Vice Chair, or the IRB Manager(s).

If an IRB member knows in advance that he or she will be absent for an extended period of time, he or she should notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the IRB. If the

member has a designated alternate, the alternate may serve during the primary member's absence, provided the IRB has been notified in advance.

The unaffiliated member(s) are required to attend at least 75% of the meetings each year. At least one member who represents the general perspective of participants is required to attend at least 75% of the meetings each year. At least one member who is knowledgeable about or experienced working with children is required for the IRB to vote on protocols that involve children and are reviewed during a convened meeting.

2.13 Training / Ongoing Education of Chair and IRB Members in Regulations, Procedures

A vital component of a comprehensive human research protection program is an education program for IRB Chair and the IRB members. Connecticut Children's is committed to providing training and an on-going educational process for IRB members and the staff of the HRPP Office, related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members will meet with the IRB Chair, HRPP Medical Director, HRPP Director, or IRB Manager(s) for an informal orientation session. At the session, the new member will be given materials which include:

- Belmont Report;
- Connecticut Children's HRPP Policies and Procedures for the Protection of Human Subjects;
- Federal regulations relevant to the IRB

Initial Education

New IRB members will also the following web-based training before they may serve as a Primary Reviewer:

- CITI IRB Member Module
- Any other modules or training specified by the HRPP office
- Peer coaching
- Presentation tools
- Reference document library

Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

Educational activities include, but are not limited to;

- In-service training at IRB meetings;
- Periodic training workshops (e.g., faculty development series);

- Copies of appropriate publications (e.g., *Human Subjects Report*, *IRB*, etc.);
- Dissemination to IRB members by the HRPP Director or IRB Chair (during IRB meetings or via email/mail) of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues.

Additionally, the Institutional Official will provide support to send as many members of the IRB as possible to attend the annual PRIM&R conference or regional OHRP conferences on human research protections.

The HRPP Office Staff shall complete the entire CITI Course in the Protection of Human Research Subjects and any other modules specified by the HRPP Director or Medical Director. Staff will be expected to attend PRIM&R or OHRP training periodically (typically annually).

2.13.1 Research funded by the Department of Defense

During the pre-review of IRB initial applications, continuing review applications, and amendments, HRPP staff will check the funding information in the protocol documents to determine if the research is DOD funded. If the research is DoD-funded, the HRPP staff will obtain documentation that the assigned reviewer(s) meet the DOD research ethics educational requirements prior to forwarding the protocol submission to the reviewer and the applicable Appendix to this document will be utilized.

2.14 Liability Coverage for IRB Members

Liability coverage for IRB members is provided under the Connecticut Children's insurance coverage, which applies to employees and any other person authorized to act on behalf of Connecticut Children's, or acts or omissions within the scope of their employment or authorized activity.

2.15 Review of IRB Member Performance

The IRB Members' performance will be reviewed on an annual basis by the Medical Director and Director of the HRPP, in consultation with the IRB Chair. Members will be provided with feedback in writing. A summary of the evaluations are provided to the Institutional Official. Members who are not acting in accordance with the IRB's mission or policies and procedures or who have an undue number of absences may receive additional training or may be removed. Criteria used to evaluate the IRB member performance include percentage of IRB meetings attended (at least 75% for primary members), contribution to IRB meetings, and completion of educational requirements. IRB members and IRB staff complete a survey about the IRB Chair; the IRB Chair receives the summary of this feedback. The HRPP Director and/or Medical Director provides a summary of the feedback to the Institutional Official.

2.16 Reporting and Investigation of Allegations of Undue Influence

If an IRB chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the HRPP Medical Director, HRPP Director, or Institutional Official, depending on the circumstances. The official receiving the report will conduct a thorough investigation and corrective action (e.g. inform responsible party of the allegation and educate regarding the perceived undue influence) will be taken to prevent additional occurrences.

3 IRB Review Process

3.1 Policy

All human subjects research conducted under the auspices of Connecticut Children's must meet the criteria for one of the following methods for review:

- Exempt
- Expedited Review
- Full Committee Review

The IRB will ensure that the research meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research.

The following describe the procedures required for the review of research by the IRB.

3.2 Definitions

Minimal Risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Minor Change. A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

- the level of risks to subjects or a change in the risk/benefit ratio
- the research design or methodology (adding procedures that are not eligible for expedited review [See Section 3.5] would not be considered a minor change)
- the number of subjects enrolled in the research
- the qualifications of the research team
- the facilities available to support safe conduct of the research
- any other factor which would warrant review of the proposed changes by the

convened IRB.

Quorum. A quorum of the IRB consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

Suspension of IRB approval: A suspension is a directive of the convened IRB or other authorized individual (See Section 3.10) to temporarily stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review.

Termination of IRB approval. A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

3.3 Human Subjects Research Determination

The responsibility for initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this initial determination based on the definitions of “human subject” and “research” in Section 1.4. Final determination rests with the IRB. Since Connecticut Children’s will hold them responsible if the determination is not correct, investigators should request a confirmation that an activity does not constitute human subjects research from the IRB through the IRBManager “Human Subject Determination Form”. This form includes common scenarios such as quality improvement activities, classroom evaluation activities, and case reports. All requests must include sufficient documentation of the activity to support the determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Section 1.4. When an activity does not meet the definition of human subjects’ research, the IRB provides the determination letter to the project team. When an activity does meet the definition of human subjects’ research, the IRB notifies the project team and provides instructions for submitting a human research application.

3.3.1 Quality Improvement Projects

The HRPP uses the following principles to determine whether a quality improvement (QI) project is research involving human subjects. Investigators must request a determination of whether a quality improvement activity constitutes human subject research from the IRB as described in Section 3.3.

- Surveys whose primary purpose is to gauge the opinions and perceptions of internal and external “customers” (trainees, staff, patients, referring physicians, and others) are an integral component of organizational quality assessment and may be considered a quality improvement activity that

does not require IRB review. Results of such surveys may yield new knowledge deserving of dissemination external to the organization through presentations and publications. Therefore, surveys performed within an institution's QI framework should not automatically require IRB consideration.

- QI projects that are designed to improve clinical care to better conform to **established/accepted standards** are not considered research.
- It may also help to think about quality improvement as activities based on existing knowledge about the enduring, nature and function of people and their environment rather than to develop new knowledge. Examples include data guided efforts to ensure adoption of evidence based on practice guideline or introduce procedures to reduce medical errors. (1)

Example Clinical practice guidelines (CPGs) are intended to increase compliance with evidence-based or consensus-based practice. In general, CPGs and other QI projects that are designed to bring care in line with evidence or consensus- based standards will not require IRB approval.

Example: Rapid cycle continuous quality improvement projects ("CQI") almost always are designed to bring care within accepted standards and may yield publishable data if conducted over a sufficient period of time for results to be statistically valid, or if the interventions are especially novel and successful. Such CQI studies almost never should require IRB review. CQI activities are often required to meet accreditation and regulatory standards.

Example: Questionnaires that are distributed to Connecticut Children's Medical Center patient and service populations for the purpose of determining their satisfaction with a service, program or clinic and for gathering information on how to improve the service, program or clinic does not require IRB review.

Example: Questionnaires or clinical de-identified databases designed to pool multi-institutional metrics for the purpose of benchmarking and reviewing individual institutional quality of care.

Source 1. Lynn, Joanne et al. The Ethics of Using Quality Improvement Methods in Health Care, *Annals of Internal Medicine* 2007; 146: 666-673;
<http://www.annals.org/cgi/content/full/146/9/666>

3.4 Exempt Studies

All research using human subjects must be approved by the institution. Certain categories of research (i.e., "exempt research") do not require convened IRB review and approval. Exempt research is, however, still subject to institutional review and exempt determinations must be made by the IRB Chair or designee of the IRB;

investigators may not make exempt determinations. Research meeting the criteria for exemption may receive an exempt designation at the discretion of the IRB Chair or Vice-Chair (or appointed IRB member). To request an exemption, an investigator completes and submits a "Request for Exemption" via the Application for Research on Human Subject form in the electronic submission system (IRBManager).

Reviewers will use the Exemption Determination Reviewer Checklist to determine and document whether the protocol meets the exemption criteria. The determination letter is provided to the investigator via the electronic submission system.

All requests for an exemption include a termination date. If the research extends beyond that date then the researcher must request review to continue the study.

3.4.1 Limitation on Research Subjects:

Vulnerable Populations:

- Children: Exemptions for research that is categorized into (1), (4), (5), (6), (7), or (8) below can be applied. Exemption for research involving educational tests or the observation of public behavior (category (2) below) can only be applied when the investigator(s) does not participate in the activities being observed.
- Prisoners: exemptions can only apply to this subject population for research aimed at a broader subject population that only incidentally includes prisoners

3.4.2 Categories of Exempt Research

With the above exceptions, research activities not regulated by the FDA (see Section 3.4.3 for FDA Exemptions) in which the only involvement of human subjects will be in one or more of the following categories are exempt from application of all regulatory criteria for approval, but require IRB assessment (which generally includes limited IRB review for privacy and confidentiality). In addition, expanded categories of exempt research as established by Connecticut Children's Medical Center IRB applies to research that is neither federally funded nor subject to FDA regulations:

1. Research conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most:
 - a) research on regular and special education instructional strategies, or
 - b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior (including visual or auditory recording), if at least one of the following criteria is met:
 - a) The information obtained is recorded by the investigator in such a

- manner that the identity of the human subjects cannot be readily ascertained, directly or through identifiers linked to the subjects; and
 - b) any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation; or
 - c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to subjects, and an IRB conducts a limited IRB review to make the determination required by 46.111(a)(7) (which refers to privacy and confidentiality)
- 3. Research involving benign* behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
 - a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
 - b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
 - c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

*For the purpose of this exemption, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research* for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*

*Secondary research is defined as research use of information or biospecimens collected for:

- Research studies other than the one proposed, or
- Non-research purposes (e.g. clinical care, public health, education)

5. Research and demonstration projects that are conducted or supported by a Federal Department or Agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstrated projects), and that are designed to study, evaluate, improve or otherwise examine:

- Public benefit or service programs including procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or
- Possible changes in methods or levels of payment for benefits or services under those programs.

Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies,
 - a) If wholesome foods without additives are consumed; or
 - b) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[The following categories are available exemptions for research, but Connecticut Children's has opted not to apply these categories]

7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and

(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

[The following expanded categories of exempt research applies to research that is neither federally funded nor subject to FDA regulations as established by Connecticut Children's Medical Center IRB]

9. In addition to research exempt under Category 2 (see above), research that involves interview or questionnaires of adults is exempt when the subjects of the research is a child, provided that:

- The risks of the research are equivalent when an adult is interviewed or administered a survey about themselves or about their child.

Limited IRB review for exempt categories

The Common Rule requires limited IRB review for select exemption categories, where the researcher retains participant's identifiable private information or use identifiable biospecimens. Connecticut Children's applies limited review to exemption categories 45 CFR 46.104 (d) (2) & (3)(i), as described above.

In limited review, the reviewer(s) is not required to apply all of the standard approval criteria listed in 45 CFR 46.111 of the regulations. The IRB reviewer conducts a limited IRB review to made the determinations required by 45 CFR 46.111 (a)(7), ensuring there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. It's important to note that this research cannot be subject to subpart D.

The IRB conducts a limited review by evaluating strategies to protect privacy and maintain confidentiality by applying equivalent protections outlined in section 3.7.5 Privacy and Confidentiality, including how the research team will:

- identify, contact and recruit subjects, how information will be access and managed, and plans for de-identification and possible re-identification of identifiable subject information or biospecimens.
- controls on storage, handling, and sharing of data, the long-range plan for protecting the confidentiality of research data, including a schedule for retention or destruction of identifiers associated with the data.

The following are elements of a limited IRB review process:

- The expedited review mechanism may be used, which means that the IRB chair or experienced IRB member performs the limited IRB review. A convened IRB can fill this function as well.
- The limited IRB reviewer only applies the specific criteria required for each applicable exempt category and determine if the applicable criteria are met.
- The IRB reviewer needs the appropriate expertise to make the required determinations. It may be appropriate to include an IT expert as a reviewer to ensure maintaining of confidentiality by use of appropriate security controls.
- The IRB reviewer who conducts limited IRB review may require modification(s) to the proposed research prior to approval or determine that the study meets the applicable

criteria and is eligible for exemption.

- There is no yearly or continuation review required for studies approved via limited IRB review.

- If the study is not eligible for the exempt category proposed, the study may be reviewed using expedited or convened IRB procedures. Limited IRB review is not a regulatory requirement for nonexempt studies.

3.4.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR 56.104(c)]; (See § 7.6.1 for more information)
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

3.4.4 Additional Protections

Exempt research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

The individual making the exemption determination will evaluate whether the research fulfills the following ethical standards:

- The research exposes participants to no more than minimal risk
- Selection of subjects is equitable
- If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data
 - To determine this, the following are considerations that the IRB would make, as applicable
 - o The nature of the identifiers associated with the data
 - o The justification for needing identifiers in order to conduct the research
 - o Characteristics of the study population
 - o The proposed use of the information
 - o The overall sensitivity of the data being collected

- o Person or groups who will have access to study data
- o The process used to share the data
- o The likely retention period for identifiable data
- o The security controls in place such as the physical safeguards for paper records, the technical safeguards for electronic records, and the secure sharing or transfer of data outside the institution, if applicable
- o The potential risk for harm that would occur if the security of the data was compromised
- If there are interactions with participants, whether there should be a consent process that will disclose such information as:
 - o That the activity involves research
 - o A description of the procedures
 - o That participation is voluntary
 - o Name and contact information for the investigator
- There are adequate provisions to maintain the privacy interests of participants.

3.5 Expedited Review

The IRB may use the expedited review procedure to review either or both of the following:

1. some or all of the research appearing on the list of categories of research eligible for expedited review unless the reviewer determines that the study involves more than minimal risk,
2. minor changes in previously approved research during the period for which approval is authorized
3. research for which limited IRB review is a condition of exemption under 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

3.5.1 Categories of Research Eligible for Expedited Review

[63 FR 60364-60367, November 9, 1998]

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity may be eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

- The expedited review procedure may not be used for classified research involving human subjects.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- The expanded categories (10) through (17) apply to research that is neither federally funded nor subject to FDA regulations.

Research Categories one (1) through seven (7) as authorized by 45 CFR 46.110 and 21 CFR 56.110 and expanded categories ten (10) through seventeen (17) as established by Connecticut Children's Medical Center IRB pertain to both initial and continuing IRB review:

- (1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - (b) from other adults and children*, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. [*Note: Children are defined in the DHHS regulations 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."][[45CFR46.402\(a\)](#)]
- (3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more

invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

(8) Continuing review of research previously approved by the convened IRB as follows:
(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
(b) where no subjects have been enrolled and no additional risks have been identified; or
(c) where the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo

subsequent continuing review by the expedited review procedure. For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.

(10) Skin biopsy not requiring suturing.

(11) Ionizing radiation exposure that does not exceed 100 mrem (1mSv) per year.

(12) Blood draws via a peripheral indwelling catheter that has been placed under standard of care, regardless of frequency.

(13) Blood sampling (that meets the NIH policy) for children that, when combined with routine standard of care blood collection, is limited to no more than 5 mL/kg on a single day or 9.5 mL/kg over the course of 8 weeks and for adults to no more than 10.5 mL/kg or 550 mL, whichever is less, over the course of 8 weeks.

(14) Obtaining additional CSF or bone marrow at the time of a clinically indicated procedure in pediatric patients weighing no less than 10 kg. Additional CSF samples are not to exceed 2mL, and additional bone marrow samples are not to exceed 5mL. No additional needle placements/insertions for research purposes are permitted under this expedited category.

(15) Obtaining additional endoscopic biopsies (not to exceed 6 additional biopsies for research purposes) during the course of a clinically indicated gastrointestinal endoscopy (lower and upper).

(16) For procedures performed for clinically indicated purposes, the excess fluid not needed for diagnostic or treatment purposes that would otherwise be discarded, obtained through the following:

a) Gastric Lavage, nasogastric tube, or gastrostomy tube;

OR

- b) Bronchoalveolar lavage (BAL) or in individuals with an existing artificial airway; endotracheal tube lavage and/or suction, or tracheostomy lavage and/or suction.

(17) Prolongation of clinically indicated sedation or general anesthesia, not to exceed 5 additional minutes and no more than once within a 52 week period (annually).

3.5.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB. The designees must be IRB committee members (either as primary or alternates). Selected reviewers will have the qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. An experienced IRB member for purposes of conducting review using the expedited procedure is an IRB member who conducted preliminary expedited reviews that were reviewed by the IRB Chair, HRPP Director, and/or the HRPP Medical Director, obtained feedback and training on the preliminary expedited reviews, and ultimately demonstrated the ability to independently conduct expedited reviews. IRB members with a conflict of interest in the research (see § 2.9) will not be selected; it is the responsibility of the IRB member to declare whether he or she has a conflict and to notify the IRB Manager(s) accordingly.

IRB members eligible to conduct expedited review will designate the appropriate expedited review category on the appropriate Reviewer Checklist. If the research does not meet the criteria for expedited review, the protocol will be placed on the next agenda for an IRB meeting for review by the convened IRB.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), should receive and review all documentation that would normally be submitted for a full-board review (including the complete protocol, a Continuation review form summarizing the research since the previous review [including modifications and adverse events], notes from any pre-screening conducted by the IRB Office staff and the current consent documentation, if any) and determine the regulatory criteria for use of such a review procedure.

IRB members conducting expedited review will follow the Review Procedures described in Sections 3.7, 3.8 & 3.9 and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth below.

Reviewers will indicate approval, required modifications or disapproval (resulting in full board review) on the appropriate Reviewer Checklist. If modifications are required the IRB Office staff will inform the investigator by letter or e-mail. If the modifications are minor, an IRB member may determine if the investigator has sufficiently addressed the modifications. If the modifications are major, or if the reviewer(s) request it, the modified protocol will be sent back to the original IRB reviewer(s) for further review.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Chair or Vice-Chair may make a final determination. Upon the discretion of the IRB Chair or Vice-Chair, the protocol will be submitted to the full IRB for review.

3.5.3 Informing the IRB

All members of the IRB will be apprised of all expedited review approvals by means of a list provided to IRB Members at regularly scheduled monthly meetings. Any IRB member can request to review the full protocol by contacting the IRB Office.

3.6 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all research at convened meetings at which a quorum (see below) of the members is present.

3.6.1 IRB Meeting Schedule

Each IRB meets on a regular basis throughout the year (usually once per month) so that there are two IRB meetings per month. The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings can be found on the Connecticut Children's IRB/HRPP website. Additionally, this information is available in the IRB/HRPP Office for the benefit of all investigators, research coordinators and other research staff when submitting protocol materials. Special meetings may be called at any time by the IRB Chair or the IRB Manager(s).

3.6.2 Preliminary Review

The IRB Operations Manager conducts pre-reviews of protocol submissions that require review at a convened IRB meeting. Only complete submissions will be placed on the IRB agenda for review. In the case of a PI who is submitting a

protocol for the first time or an investigator who may not be well-versed in the protocol submission procedures, individualized IRB consultations can be arranged. Specific questions about the IRB policies and procedures, determination of whether a particular protocol is human research or not and what particular forms are required for a particular study can be submitted in writing to the HRPP Director or IRB Manager(s) for information and/or clarification. Individual appointments with the HRPP Director or IRB Manager(s) can also be arranged and are strongly recommended for first- time submissions.

3.6.3 Primary and Secondary Reviewers

After it has been determined that the protocol submission is complete, the IRB Operations Manager, with the assistance of the IRB Chair as needed, will assign protocols for review paying close attention to the scientific content of the protocol and the potential reviewer's area of expertise. A primary and a secondary reviewer will be assigned to each protocol and a reviewer may be assigned several protocols or other research items for review. Reviewers are assigned to all protocols requiring initial review, continuing review, and modifications. When the IRB is presented with a protocol which may be outside of the knowledge base of any of the IRB members, an outside consultant will be sought. (See Section 2.10 above)

The primary and secondary reviewers are responsible for:

1. The primary reviewer has a thorough knowledge of all of the details of the proposed research and leads the discussion.
2. Performing an in-depth review of the proposed research.
3. Presenting both positive and negative aspects of the research, and leading the IRB through the regulatory criteria for approval (See Section 3.7).
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms.

If the primary or secondary reviewer is absent from the meeting, a new reviewer may be assigned, providing the new reviewer has reviewed the materials prior to the meeting. Additionally, an absent reviewer can submit written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary or secondary reviewer. It should be noted that all of the IRB members receive and are expected to review all studies, not just the ones they are responsible for reviewing.

3.6.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted (in full) 3 weeks prior to the convened meeting for inclusion on the following IRB agenda. The meeting agenda will be prepared by the IRB staff under the supervision of the HRPP Director and IRB Manager(s) and distributed to the IRB members prior to the meeting. All IRB members

receive their review materials (or access to the materials in the on-line electronic system, IRBManager) no later than 5 business days before the scheduled meeting to allow sufficient time for the review process. Review materials include the IRB agenda, protocol review materials, the prior month's meeting minutes (if available), and other applicable business items and audits, as well as any appropriate continuing education materials.

3.6.5 Materials received by the IRB

Each IRB member receives and reviews the following documentation, as applicable, for all protocols on the agenda:

1. Complete IRB Protocol Application form
2. Complete protocol which includes:
 - a. Objectives
 - b. Background
 - c. Study design
 - d. Inclusion/exclusion criteria
 - e. Statistical methods
2. Proposed Consent / Parental Permission / Assent Form(s)
3. Recruitment materials / subject information
4. Data collection instruments (including all surveys and questionnaires)
5. For modifications on the agenda, each IRB member receives and reviews all modified documents.

At least one primary reviewer must receive and review the following (when one exists): the sponsor's protocol; the investigator's brochure; the DHHS-approved sample informed consent document; the complete DHHS-approved protocol.

The Chair or Vice-Chair will have access to grant applications/contracts, as needed. Any IRB Member may review any of the material provided to the primary and secondary reviewers by accessing it in the electronic submission system or by contacting the IRB Office.

If an IRB member requires additional information to complete the review they may contact the investigator directly or may contact the IRB Office to make the request of the investigator.

Protocol reviewers will use the Reviewer Checklist as a guide to completing their review.

3.6.6 Quorum

A quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate

quorum is present before calling the meeting to order. The IRB Chair will be responsible to ensure that the meetings remain appropriately convened.

A quorum must be maintained for each vote to occur. The IRB Manager(s) and the IRB Coordinator/Analyst take notes of arrivals and departures of all members and notifies the chair if a quorum is not present. If a quorum is not maintained, the proposal must be deferred or the meeting must be terminated.

Members are considered present if participating through teleconferencing or videoconferencing. In order to be able to vote, in such cases the member must have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

3.6.7 Meeting Procedures

The IRB Chair, or Vice-Chair in the event that the IRB Chair is absent, will call the meeting to order, once it has been determined that a quorum is in place. The Chair or Vice-Chair will remind IRB members to recuse themselves from the discussion and vote by leaving the room where there is a conflict. The IRB will review and discuss the IRB minutes from the prior meeting, if available, and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The primary and secondary reviewer present an overview of the research and lead the IRB through the completion of the regulatory criteria for approval in the Reviewer Checklist. All members present at a convened meeting have full voting rights, except in the case of a conflict of interest (see below). In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB Manager to take notes and write the minutes for each IRB meeting.

3.6.8 Guests

At the discretion of the IRB, the Principal Investigator may be invited to the IRB meeting to answer questions about their proposed or ongoing research. The Principal Investigator may not be present for the discussion or vote on their research.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair or Vice-Chair. Guests must agree to keep the proceedings and deliberations of the meeting confidential.

3.7 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects' research for initial review, continuing review, and review of modifications approved through expedited or the convened IRB it must determine that the following requirements are satisfied:

- (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
- (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR § 46.116.
- (5) Informed consent will be appropriately documented or appropriately waived in accordance with, and to the extent required by 45 CFR §46.117.
- (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- (8) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

3.7.1 Risk/Benefit Assessment

The goal of the risk/benefit assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society. Toward that end, the IRB must:

1. judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;
2. disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the IRB - involves a series of steps:

1. **identify the risks** associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
2. **determine whether the risks will be minimized** to the extent possible;
3. **identify the probable benefits** to be derived from the research;
4. **determine whether the risks are reasonable in relation to the benefits** to subjects, if any, and assess the importance of the knowledge to be gained;

Risks to subjects are minimized:

1. by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
2. whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Risks to subjects are reasonable in relation to anticipated benefits, if any, and to the importance of the knowledge that may reasonably be expected to result:

1. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research - as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.
2. The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Research studies have resources necessary to protect participants, including

1. Adequate time for the researchers to conduct and complete the research;
2. Adequate number of qualified staff;
3. Adequate facilities;
4. Access to a population that will allow recruitment of the necessary number of participants; and
5. Availability of medical or psychosocial resources that participants may need as

a consequence of the research.

When the Connecticut Children's researcher is the lead researcher of a multi-site study, the IRB shall evaluate whether the management of information that is relevant to the protection of participants is adequate.

3.7.1.1 Scientific Merit

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or the IRB may draw on the knowledge and disciplinary expertise of others, such as the Scientific Review Committee, reviews by a funding agency, or departmental review.

When considering multi-center trials, (e.g. large clinical trials), the IRB relies upon its own expertise to establish scientific merit (the primary reviewer completes the IRB Reviewer checklist which addresses issues of scientific design). For investigator-initiated, non-multi-center research, and non-industry sponsored research, the IRB receives and considers the recommendations of the Scientific Review Committee. In addition, the IRB primary reviewer also completes the IRB Reviewer Checklist which addresses issue of scientific design. In all cases, the IRB makes final determinations regarding the scientific or scholarly validity of a proposed research study.

3.7.2 Selection of subjects is equitable.

The IRB determines by viewing the application, protocol and other research project materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates: the purposes of the research; the setting in which the research occurs; scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, persons with intellectual disabilities, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; the inclusion/exclusion criteria; participant recruitment and enrollment procedures; and the influence of payments to participants.

At the time of the continuing review the IRB will determine if the PI has followed the subject selection criteria that he/she/ originally set forth at the time of the initial

IRB review and approval.

3.7.2.1 Recruitment of Subjects

The PI will provide the IRB with all recruiting materials to be used in identifying participants including recruitment methods, advertisements, and payment arrangements. (See Section 3.8.7 regarding IRB review of advertisements; Section 3.8.8 regarding IRB review of payments to subjects.)

3.7.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. (See Section 5 below for detailed policies on informed consent.)

3.7.4 Data Safety Monitoring

The IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. For research in which risks are substantial, the IRB may require a general description of the data and safety- monitoring plan to be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events (AEs). In general, it is desirable for a Data and Safety Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) requires a DSMB. The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

When determining whether a research plan makes adequate provisions for monitoring data, the IRB may consider the following factors:

1. What safety information will be collected, including serious adverse events;
2. How the safety information will be collected (e.g., at study visits, by telephone calls with participants, with case report forms);
3. The frequency of data collection, including when safety data collection starts;
4. The frequency or periodicity of review of cumulative safety data;
5. Whether a data monitoring committee has been established and the plan

6. for reporting the committee's findings to the IRB and the sponsor;
Which conditions will trigger an immediate suspension of the research, if applicable?

3.7.5 Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to **protect the privacy** of subjects and to **maintain the confidentiality of the data**.

Definitions

Privacy - having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

Confidentiality - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.

Private information - information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Identifiable information – information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to subjects or subjects' private, identifiable information and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information. In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential participants
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about participants and the nature of the requested information
- Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study.

Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the PI, can readily

ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential for harm from inappropriate disclosure.

At the time of initial review, the IRB ensures that the privacy is protected. The IRB assesses whether there are adequate provisions to maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information:

- a. About subjects,
- b. About individuals who may be recruited to participate in studies
- c. The use of personally identifiable records and
- d. The methods to protect the confidentiality of research data.

The PI will provide the information regarding confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether or not confidentiality of research subjects is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 16.1).

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and/or other relevant factors in determining the adequacy of confidentiality protections.

3.7.6 Vulnerable Populations

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 6.

3.8 Additional Considerations during IRB Review and Approval of Research

3.8.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocols. For research with children

(nearly all of the research at Connecticut Children's), the IRB makes the appropriate risk/benefit determinations specified in Subpart D of the federal regulations (e.g. 45 CFR 46.404; 45 CFR 46.405, etc.). Risks associated with the research will be classified as either "minimal" or "greater than minimal" based on the "absolute" interpretation of minimal risk. The meeting minutes will document the IRB's determinations regarding risk/benefit.

3.8.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols. All protocols requiring review by the convened IRB will be reviewed at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the IRB's determination regarding review frequency.

3.8.2.1 Review More Often Than Annually

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

1. Significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
2. The involvement of especially vulnerable populations likely to be subject to coercion.
3. A history of serious or continuing non-compliance on the part of the PI. The following factors will also be considered when determining which studies require review more frequently than on an annual basis:
 - a. The probability and magnitude of anticipated risks to subjects.
 - b. The likely medical condition of the proposed subjects.
 - c. The overall qualifications of the PI and other members of the research team.
 - d. The specific experience of the PI and other members of the research team in conducting similar research.
 - e. The nature and frequency of adverse events observed in similar research at this and other institutions.
 - f. The novelty of the research making unanticipated adverse events more likely.
 - g. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one (1) year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one (1) year.

3.8.3 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator, that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. Protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by Principal Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
3. Protocols randomly selected for internal audit.
4. Whenever else the IRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

3.8.4 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an

impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

See Section 5.10 for a detailed discussion of consent monitoring.

3.8.5 Investigator Conflicts of Interest

The research application asks research personnel to review and amend, as necessary, their financial interest disclosures. As part of its review process, the IRB will make a determination as to whether a conflict of interest exists with regard to the research under review. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict management plan that adequately protects the human subjects in the protocol is in place. (For a complete discussion of Connecticut Children's policy regarding conflicts of interest in research, please refer to Section 13 of this Manual).

3.8.6 Significant New Findings

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The PI must report any significant new findings to the IRB and the IRB will review them with regard to the impact on the subjects' rights and welfare. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the PI contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The informed consent should be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

3.8.7 Advertisements

The IRB must approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the Connecticut Children's IRB. The IRB will review:

1. The information contained in the advertisement.
2. The mode of its communication.
3. The final copy of printed advertisements.

4. The final audio/video taped advertisements.

This information should be submitted to the IRB with the initial application or as an addendum to the protocol.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic. Materials should not create an undue influence on the subject to participate, such as (but not limited to):

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol;
2. Claims, either explicitly or implicitly, about the drug, biologic or device that are inconsistent with FDA labeling;
3. Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic or device;
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational;
5. Promising “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation;
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media;
7. Statements which include promises of a discounted product once the study is completed (e.g., a coupon good for a discount on the purchase price of a product once it has been approved for marketing);

8. Exculpatory language

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the clinical investigator and/or research facility;
2. The condition being studied and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. The time or other commitment required of the subjects;
5. The location of the research and the person or office to contact for further information;
6. A clear statement that this is research and not treatment;
7. A brief list of potential benefits (e.g. no cost for health exam).

3.8.8 Payment to Research Subjects

Payment to research subjects may be an incentive for participation or a way to reimburse a subject for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid coercion of subjects. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

The IRB must review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. The IRB does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive.

The consent form must describe the terms of payment and the conditions under which subjects would receive partial payment or no payment (e.g., if they withdraw from the study before their participation is completed). Identifying information will be needed to issue checks, cash, or gift certificates to subjects. The consent form must inform subjects what information they will be asked to provide (e.g., Social Security Number, verification of U.S. Citizenship or Permanent Resident Status, etc.) to receive payment.

3.8.9 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from researchers (physicians) (“finder’s fees”) is not permitted. Similarly payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (“bonus payments”) are also not permitted. Reimbursement for physician time involved in screening potential subjects may be allowed; PIs are encouraged to review such arrangements in advance with the IRB Chair, HRPP Medical Director, or HRPP Director.

3.8.10 Compliance with all Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and the IRB rely on the Legal Department as needed for the interpretation and application of Connecticut State law and the laws of any other jurisdiction where research is conducted as they apply to human subjects’ research.

All consent forms must be consistent with applicable state and local laws.

3.9 Possible IRB Actions

Approval - the study is approved as submitted.

Approval Contingent upon clarification of non-substantive issues - the protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided. When the needed revisions are agreed upon at the meeting after they are designated by the reviewer(s), these revisions are presented to the Principal Investigator for incorporation by simple concurrence and reviewed by expedited procedure.

In order to receive approval for a protocol contingent upon clarification of non-substantive issues:

1. For full review, the investigator's response, the revised protocol and the previously submitted protocol is given to the IRB Operations Manager, IRB Chair, Vice Chair, or a subcommittee of the IRB for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the IRB.
2. For expedited, the investigator's response, the revised protocol and the previously submitted protocol is given to the same reviewer(s) for re-review.
3. Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).
4. The outcome of the IRB's deliberations is once again communicated to the investigator in writing.
5. The IRB's determination concerning the subsequent amended submission will be documented in the file.

Note: For full review, the expiration date for the protocol is calculated based on the date that the convened IRB reviewed the protocol and NOT on the final approval date.

Approval contingent upon clarification of substantive issues - This action is taken if specific substantial modification or other clarification regarding the protocol and/or consent form is required. "Substantive" issues include those that affect one or more of the regulatory criteria for approval. IRB approval of the proposed research must not occur until there has been subsequent review of the material submitted by the PI by the convened IRB.

In order to receive approval for a protocol contingent upon clarification of substantive issues:

1. For protocols reviewed by the convened IRB, the PI's response must be submitted for review at a subsequent, convened meeting of the IRB. The IRB Office provides the IRB with the PI's response, the revised protocol and the previously submitted protocol. The item is placed on the agenda for re-review at the next meeting.
2. Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

3. The outcome of the IRB's deliberations is once again communicated to the PI in writing.
4. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the IRB meeting or in the file for expedited review.

Note: For full review, the date of approval is the date when the conditions were determined to be met and the expiration date for the protocol is calculated based on the date that the convened IRB reviewed the responsive material from the investigator and determined that no further substantive clarifications were required.

Deferred /Tabled - Insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). The IRB will notify the PI of the specific concerns identified by the IRB. The PI may make changes that address the IRB's concerns and re-submit the study at a later date.

Disapproved - The IRB has determined that the research cannot be conducted at Connecticut Children's or by employees or agents of Connecticut Children's or otherwise under the auspices of Connecticut Children's.

Approval in Principle. As per federal regulations, (45CFR46.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents. One is if study procedures are to be developed during the course of the research, but human subjects' approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests. Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

3.10 Study Suspension, Termination and Administrative Hold

3.10.1 Suspension/Termination

The IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unanticipated problems or serious harm to subjects. (See Section 8 for a discussion of unanticipated problems and Section 9 for a discussion of non-compliance)

Suspensions or terminations are reported in accordance with reporting requirements (See Section 10 Reporting to Regulatory Agencies and Institutional Officials).

Suspension of IRB approval is a directive of the convened IRB, IRB Chair, HRPP Director or Medical Director either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

The IRB Chair, HRPP Director, or Medical Director may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair, HRPP Director, or Medical Director must be reported to a meeting of the convened IRB.

Research may only be terminated by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will notify any subjects currently participating that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

3.10.2 Administrative Hold

An investigator may request an administrative hold on a protocol when the investigator wishes to temporarily or permanently stop some or all approved research activities. An administrative hold may be initiated by an investigator. Administrative holds are not suspensions or terminations, and therefore the reporting requirements for suspensions and terminations do not apply.

Administrative hold is defined as follows:

- A voluntary interruption of research enrollments and ongoing research activities by the investigator
- Does not apply to interruptions of research related to concerns regarding safety, right, or welfare of human research participants, research investigators, research staff, or others
- Will not be used to avoid reporting deficiencies or circumstances that otherwise require reporting by federal agencies
- Cannot be used to extend IRB approval beyond the expiration date of a protocol without IRB approval of continuing review

3.10.2.1 Procedures

1. Investigators must notify the IRB in writing that:
 - a. They are voluntarily placing a study on administrative hold in response to a request by the convened IRB or IRB designee
 - b. A description of the research activities that will be stopped
 - c. Proposed actions to be taken to protect current participants. Actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate harm, or alteration of protocol procedures.
2. Upon receipt of written notification from the investigator, the IRB Manager(s) or HRPP Director notifies the IRB Chair, HRPP Medical Director, (and HRPP Director, if needed) and places the research on the IRB meeting agenda for review.
3. The IRB Chair, in consultation with the HRPP Medical Director and/or HRPP Director, and the investigators, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants as described below (see Section 3.10.3).
4. The IRB Chair, in consultation with the HRPP Medical Director and HRPP Director, and investigator(s), determines how and when currently enrolled participants will be notified of the administrative hold.
5. Investigators may request a modification of the administrative hold by submitting a request for a modification to previously approved research.

3.10.3 Protection of Currently Enrolled Participants

Before an administrative hold, termination, or suspension is put into effect, the

convened IRB or IRB designee considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another investigator
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of participants for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current participants
- Notification of former participants

3.11 Continuing Review

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate for each research protocol:

- The frequency of research requiring review by the convened IRB will not be less than once per year.
- Unless an IRB determines otherwise, continuing review is not required when:
 - o Research is eligible for expedited review
 - o Research reviewed by the IRB in accordance with the limited IRB review required by specific exemption categories
 - o Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
 - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

3.11.1 Approval Period

Determination of the approval period and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur or approval might be subject to a review of study performance after a few months of enrollment, or after enrollment of the first several subjects.

For each initial or continuing approval the IRB will indicate an approval period with an approval expiration date specified:

- For studies requiring continuing review: the expiration date, unless otherwise noted by the IRB, is one year minus one day from the date that

the study was initially approved by the convened IRB or expedited reviewer.

- o IRB approval is considered to have lapsed at midnight on the expiration date of the approval.
 - o For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB voted for approval as submitted or approval contingent upon minor clarifications of non-substantive issues. (Studies for which the IRB grants approval contingent upon substantive clarifications must return to the full board for re-review, and the approval period does not start until the IRB subsequently votes for approval as submitted or approval contingent upon minor clarifications of non-substantive issues.)
 - o For a study approved under expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol
- For studies that do not require continuing review: studies will be approved for either the anticipated timeline of the project, as designated in the IRB Application, or for one year from the date of approval, whichever is greater
 - o Investigators may extend the approval period by submitting an amendment to the expected timeline of the project
 - o Research cannot be conducted beyond the stated approval period

The approval date and approval period are clearly noted on all IRB approval letters sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires.

3.11.2 Continuing Review Process

It is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. To assist investigators, the IRB Office staff will send out renewal notices (via the electronic system, IRBManager) to investigators in advance of the expiration date. For protocols that require full board review, reminders are sent at 70 days and 60 days prior to expiration; for protocols that are eligible for expedited continuing review, reminders are sent at 45 days and 30 days prior to the expiration date. **By federal regulation, no extension to the approval expiration date can be granted.**

Investigators must submit the following for continuing review:

- current consent document;
- any newly proposed consent document; and
- the continuing review report which requires a status report on the progress of the research including:
 - The number of participants accrued
 - A summary since the last IRB review of:
 - o Adverse events and adverse outcomes experienced by participants
 - o Unanticipated problems involving risks to participants or others
 - o Participant withdrawals
 - o The reasons for the withdrawals
 - o Complaints about the research
 - o Amendments or modifications
 - o Any relevant recent literature
 - o Any interim findings
 - Any relevant multi-center trial reports
 - The researcher's current risk- potential benefit assessment based on study results

In conducting continuing review of research not eligible for expedited review, all IRB members are provided and review all of the above material and the primary reviewer will review the complete protocol, including any modifications previously approved by the IRB. At the meeting, the primary and secondary reviewers lead the IRB through the completion of the regulatory criteria for approval in the appropriate Reviewer Checklist. IRB Office staff attend the convened meetings and the complete protocol files for each protocol on the agenda are available for review. The IRB staff will retrieve any additional related materials requested by IRB members.

In the case of expedited review, the IRB members may request the IRB office staff to provide them with any additional materials required for the review.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document. During continuing review of protocols, the IRB shall make the following determinations:

- whether the protocol needs verification from sources other than the researchers that no material changes had occurred since previous IRB review
- whether there are any significant findings that arise from the review process that may relate to participants willingness to continue to participate in the study
- if the consent form is still accurate and complete.

3.11.3 Expedited Review of Continuing Review

The IRB Chair designates the IRB members who may conduct review using the expedited procedure. In conducting continuing review under expedited review, the reviewers receive all of the above material. The reviewer(s) complete the Reviewer Checklist as appropriate to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 (see Expedited Review Categories). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

3.11.4 What Occurs if There is a Lapse in Continuing Review?

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If the review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. **This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.**

The IRB Office is responsible for immediately notifying the investigator of the expiration of approval and that all research activities must stop. If research participants are currently enrolled in the research project and their participation is ongoing, the PI must immediately submit to the IRB Chair (once notified that approval has expired) a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so.

Failure to submit information on time for studies in which research activities are continuing is non-compliance and will be handled according to the non-compliance policy (See Section 10, Complaints and Non-Compliance).

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 45 days and the PI has not provided the required continuing review information, the IRB will assess whether the PI must submit a new application to the IRB for review and approval or if the existing materials can be reviewed for continued IRB approval. If the study approval has lapsed

45 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If a research protocol receives contingent approval at the time of the continuing review and the approval expires before the PI responds to the contingencies, the PI may not enroll any new subjects or access medical records after the approval expiration date. Once the PI responds, the existing protocol will be reviewed for continuation. If the PI does not respond for an extended period, the IRB may vote to administratively close the study. Decisions of this kind must be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing treatment as part of the research study.

3.12 Amendment of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes in approved research** - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once). The approval letters for initial and continuing reviews include a statement that the investigator must seek IRB approval before making any changes in approved research. Furthermore, the CITI training modules mention the requirement for investigators to obtain IRB approval prior to implementing changes to research during the period for which IRB approval has already been given.

Modifications may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to add a population and revise study procedures, the IRB might require a new application for human subjects' approval. The IRB will make determinations regarding what falls within the scope of what the IRB originally authorized on a case by case basis.

Investigators must submit documentation to inform the IRB about the changes in the status of the study, including, but necessarily limited to:

- Completed Amendment Application
- Revised Investigator's protocol application or sponsor's protocol (if applicable)
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study
- Revised or additional recruitment materials
- Any other relevant documents provided by the investigator

IRB Office staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants full board review. The reviewer(s) using the expedited procedure

has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the protocol for full board review.

3.12.1 Expedited Review of Protocol Modifications

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or designee(s) among the IRB members. Minor changes include procedures that are not greater than minimal risk and do not alter the risk/benefit ratio, or those that fall within the expedited review categories (1) through (7) as described in Section 3.5.1. Modifications involving procedures that involve greater than minimal risk or which alter the risk-benefit ratio may not be approved using expedited review procedures.

The reviewer(s) receive and review the same materials that the convened IRB receives for protocols reviewed by the convened IRB. The reviewer(s) complete the appropriate Reviewer Checklist” to determine whether the modifications meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed modifications meets the regulatory criteria for approval.

3.12.2 Full Board Review of Protocol Modifications

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed (no longer than within 30 days) of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members are provided with and review all documents provided by the investigator.

At the meeting, the primary reviewer presents an overview of the modifications and leads the IRB through the completion of the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to participants. The IRB also determines whether the research with the proposed modifications meets the regulatory criteria for approval.

3.13 Closure of Protocols

The completion of the study and plans to stop all research activities regardless of whether the study is complete must be reported to the IRB. The study should be closed when the research no longer involves interaction or intervention with the participant, the collection of identifiable information, releasing identifiable information and analyzing identifiable private information. Investigators are required to submit a Study Closure Form to the IRB when the study is complete or the investigator plans to stop all human subject research activities.

IRB staff will review the closure application for completeness.

3.14 Reporting IRB Actions

All IRB actions are communicated to the PI, or designated primary contact person for the protocol, in writing within ten (10) working days via a letter prepared by the IRB staff and signed by the IRB Chair or designee. For an approval, along with written notification of approval, a copy of the approved consent form containing the stamped approval with the dates of the approval and expiration on each sheet will be sent to the investigator. For a contingent approval, the notification will include the modifications required for approval along with the basis for requiring those modifications. For a deferral, disapproval, termination or suspension, the notification will include the basis for making that decision.

All letters to investigators must be filed in the protocol files maintained by the IRB. The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the Institutional Official and are stored permanently and securely in the IRB Office.

3.15 Appeal of IRB Decisions

When a protocol qualifies for review using the expedited procedures but the reviewer concludes that disapproval may be warranted, the research proposal will be referred to the full IRB for review at its next convened meeting. In the event of a dispute regarding a contingency required for approval in the context of expedited review, the PI may request review by the convened IRB.

When an IRB protocol presented at a convened meeting is disapproved, deferred, or granted approval contingent upon modifications, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

In cases where there is disagreement between the IRB and the PI regarding the nature and extent of the requested changes and these disagreements cannot be resolved amicably in an informal manner, the PI and/or the IRB may make an appeal to the IO

for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the PI. While the IO may provide input and make recommendations to the IRB for expeditious resolution of the matter, final recommendations for approval remain under the purview of the IRB. The results of any discussions with the IO will be reported to and considered by the convened IRB at the next scheduled meeting. The IRB may choose to reconsider the protocol based on any new information presented or if warranted under the circumstances. In all cases, the IRB makes the final decision regarding the approval or disapproval of the research.

4 Documentation and Records

4.1 Policy

Connecticut Children's shall prepare and maintain adequate documentation of the IRB's activities. All records must be accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

4.2 IRB Records

IRB records include, but are not limited to:

- Research protocols
- Investigators' brochures, if any
- Recruitment materials
- Scientific evaluations (if any) that accompany the proposals
- Approved consent documents, including DHHS-approved sample consent document and protocol, when they exist
- HIPAA Authorization documents if separate from the informed sample consent documents
- Records of continuing review activities, including progress reports submitted by investigators, including the rationale for conducting continuing review of research that otherwise would not require continuing review
- Any proposed amendments and the IRB action on each amendment
- Reports of injuries to subjects and serious, unexpected adverse events, and unanticipated problems involving risks to subjects or others
- Data and safety monitoring reports, if any
- Modifications to previously approved research
- Documentation of protocol violations

- Documentation of non-compliance with applicable regulations
- Statements of significant new findings provided to subjects
- IRB membership roster(s)
- IRB meeting minutes
- Copies of all correspondence between the IRB and the investigator
 - Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of the regulations

IRB records must also document any determinations required by the regulations and protocol-specific findings supporting those determinations, including:

- Research involving children.
- Waiver or alteration of the consent process.
- Research involving pregnant women, fetuses, and neonates.
- Research involving prisoners.

IRB records for initial and continuing review of research by the expedited procedure include:

- The justification for the using the expedited procedure.
 - The rationale for an expedited reviewer's determination that the research appearing on the expedited review list is more than minimal risk and thus requires convened IRB review
- Actions taken by the reviewer
- Any findings required by laws, regulations, codes, and guidance to be documented

IRB records include justification for exempt determinations.

4.3 IRB Membership Roster

A membership list of IRB members must be maintained; it must identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list must contain the following information about members:

1. Name
2. Earned degrees
3. Affiliated or non-affiliated status (neither the member nor an immediate family member of the member may be affiliated with Connecticut Children's)
4. Status as scientist (physician-scientist, other scientist, non-scientist) for

purposes of this roster, IRB members with research experience are designated as scientists (including any student member). Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research. Students being trained in research fields will be designated as scientists.

5. Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; such as which IRB members are knowledgeable about or experienced in working with children, or other vulnerable populations locally involved in research; as well as which IRB member is a prisoner representative (as required by Subpart C)
7. Role on the IRB (Chair, Co-Chair, etc.)
8. Voting status (Any *ex officio* members are non-voting members)
9. Alternate status, including the member they alternate with
10. Relationship (e.g., employment) between the individual IRB member and the organization

The HRPP office must keep the IRB membership list current. The HRPP Director, or designee, must promptly report changes in IRB membership to the Office for Human Research Protections, Department of Health and Human Services.

4.4 The IRB Minutes

Proceedings must be written and approved by the convened IRB, and are generally available for review by the next regularly scheduled IRB meeting date. Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
 - a. Names of members present
 - b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions.
 - c. Names of absent members
 - d. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster)
 - e. Names of consultants present
 - f. Name of investigators present
 - g. Names of guests present

Note: The initial attendance list shall include those members present at the meeting. The vote on each action will reflect those members present for the vote on that item.

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. Business Items discussed
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
6. Votes on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those excused, Number of those recused)
7. Basis or justification for these actions including required changes in research
8. Summary of any controverted issues and their resolution
9. Approval period for initial and continuing approved protocols
10. Determination of whether re-consent is required for modifications to research.
11. Risk level of initial and continuing approved protocols
12. Applications that have met or not met the stipulations specified in contingent approvals;
13. Justification of deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document (if any).
14. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.116(d)] when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent
15. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived
16. When approving research that involves populations covered by Subparts D (children), B (pregnant women, human fetuses, and neonates), or C (prisoners) of 45 CFR 46, or research involving participants with diminished capacity, the Minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.
17. The rationale for significant risk/non-significant risk device determinations for research involving investigational devices.
18. Determinations of conflict of interest.
19. Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with intellectual disabilities, or economically or educationally disadvantaged persons, regardless of source of support for the research.

20. A list of research approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol.
21. Documentation of approval by the Chair or designee of research approved contingent upon minor clarifications. Documentation of approval should be noted in the Minutes of the next IRB meeting that occurs after the date of the approval.
22. An indication that, when an IRB member has a conflicting interest (see Section 2.9) with the research under review, the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained.
23. When IRB Members recuse themselves from the final deliberation and vote on a research study due to a conflict, their names and the nature of their conflict is noted in the minutes and the reason for their departure is documented as a recusal due to a conflict of interest.
24. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant

A copy of the IRB-approved minutes for each IRB meeting will be distributed to the Institutional Official. The IRB minutes, once approved, can only be altered without formal concurrence and approval of the convened IRB for purely administrative or grammatical errors. Any other changes required concurrence and approval of the convened IRB (e.g., to correct factual or typographical errors).

4.5 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request for exemption satisfies the conditions of the cited exemption category and meets the requirements as set forth in section 3.4. The exempt determination is reported at the next convened IRB meeting and documented in the Minutes.

4.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; a description of action taken by the reviewer; the rationale for requiring continuing review, the approval period, and any determinations required by the regulations including protocol- specific findings supporting those determinations.

4.7 Record Retention

The above detailed records must be stored securely in the IRB Office, IRBManager or a storage facility and must be retained for at least 3 years after

study closure.

IRB records not associated with a specific research study, or for protocols cancelled without participant enrollment, will be retained at the facility for at least 3 years (after study closure, when applicable).

All records must be accessible for inspection and copying by authorized representatives of the OHRP, FDA, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

Records are maintained in locked file cabinets and/or locked offices within the IRB Office, computer-based files with access privileges/passwords, IRBManager or a storage facility and are available only to IRB members and IRB/HRPP office staff.

4.8 Investigator Records

PIs are required to maintain records of their human subjects' research activities. In general, PIs should establish a file for each study that has been reviewed by the IRB. These files should closely resemble the IRB's files on the study.

In general, PIs should maintain a file for each subject who signs a consent document agreeing to participate in the study. These subject specific files should include the signed consent document/documentation of verbal consent, and copies of case report forms, and any other correspondence between the PI and the subject.

Research records should be maintained for a duration that is appropriate to the type of study. For research in which multiple regulations/requirements apply, Investigators should apply the longest applicable standard. External Sponsors may have a longer requirement than noted below.

Investigator Study Records Regulatory Retention Requirements	
Type of Records	Minimum Retention Period
IRB Records	3 years after study completion
FDA Regulated Research	2 years after last marketing approval
Federally Funded Research	3-7 years after expiration of grant period
Other Research	3-6 years after study completion
HIPAA Authorization & Waiver	6 years after completion of study

4.8.1 FDA Regulated Studies

Investigational Drugs

Investigators are expected to conduct the study in accordance with the plan agreed upon by the sponsor and approved by the IRB. The requirements for such records are found in regulation 21 CFR 312.62(a)(b)(c), such as:

(a) Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under Sec. 312.59.

(b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including (for example) signed and dated consent forms and medical records (e.g., progress notes of the physician, the individual's hospital chart(s), and the nurses' notes). The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Investigational Devices

The Investigators are expected to conduct the study in accordance with the plan agreed upon by the sponsor and approved by the IRB. The study must be conducted under the supervision of the investigator. Investigational devices may not be supplied for use to any investigator not authorized under the approved IRB protocol. In addition, investigators must maintain records of the investigation as detailed below and found in the federal regulation 21 CFR 812.140(a)(d):

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: (1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to: (i) the type and quantity of the device, the dates of its receipt, and the batch number or code mark; (ii) the names of all persons who received, used, or disposed of each device; (iii) why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records (including, e.g., progress notes of the physician, the individual's hospital chart(s), and the nurses' notes). Such records shall include: (i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician

and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study. (ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests. (iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

4.8.2 Federally Funded Studies

Investigators are expected to conduct the study in accordance with the plan agreed upon by the federal agency and approved by the IRB. The requirements for such records are found in regulation 2 CFR 200, Subpart D §200.334, which includes regulations for record retention and access to records for awards to recipients. The other records pertinent to an award includes all research-related study records. The minimum retention period is 3 years but individual granting agencies can require longer periods of up to 7 years. Investigators must comply with the requirements of the granting agency.

4.8.3 Studies subject to the Health Insurance Portability and Accountability Act (HIPAA)

Investigators are expected to conduct the study in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and as determined by the IRB. The requirements for such records are found in regulation 45 CFR 164.530(j).

Documentation of Written and Verbal HIPAA Authorization, IRB Determinations for Waiver of HIPAA and Disclosures of PHI must be retained for a 6 year period after the date of its creation or the date when it was in effect, which is later. If the written authorization indicates an expiration date, the Investigator must retain the HIPAA Authorization for 6 years beyond the expiration date.

5 Obtaining Informed Consent/Parental Permission/Assent to Participate in Research

5.1 Policy

It is the policy of Connecticut Children's to comply with all federal and state laws and regulations that pertain to informed consent, parental permission, and assent.

No investigator conducting research under the auspices of Connecticut Children's may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 5.11 of these procedures. Except as provided in Section 5.11 of these procedures, informed consent/parental permission must be documented by the use of a written consent form approved by the IRB (See Section 5.9). The IRB will evaluate both the consent process and the procedures for documenting informed consent/parental permission to ensure that adequate informed consent is obtained from participants.

5.2 Definitions

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

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. According to Connecticut state law, minors are persons under the age of eighteen (C.G.S. Section 1-1(d)). The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, the Connecticut Children's IRB generally defines children as persons under eighteen years of age. Connecticut law, however, provides minors the right to seek medical care and treatment without the consent of a parent/legal guardian in certain situations in some circumstances, as follows:

- 1) Emancipated minors are able to consent to their own medical care in all situations, therefore, they do not meet the definition of "children" under Subpart D. (Connecticut law enumerates certain categories of individuals age 16 or older who may initiate procedures for emancipation, which includes 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.; see C.G.S Section 46b-150 et seq.). Emancipated individuals do not meet the federal definition of children and therefore Subpart D requirements do not apply;
- 2) Minors in Connecticut may seek medical care for certain conditions specified in state law without parental consent, as further described below. While Subpart D would apply, parental permission may be waived if the research is limited to such conditions:
 - i. Individuals under 18 years of age may seek HIV testing, counseling, and treatment for HIV (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-601) without parental consent. However, this does not equate to legal capacity to consent. Except for HIV testing and counseling and treatment for sexually transmitted diseases, the right to seek treatment without parental consent is generally subject to certain determinations by the physician (e.g. that requiring parental consent would not be in the minor's best interest or would cause the minor to refuse treatment).

- ii. Minors 14 years of age or older may consent to inpatient mental health admission on their own behalf (17a-79) (parents must be notified of admission within 24 hours). For purposes of inpatient mental health services, a "minor" is considered an individual under the age of 16;
- iii. Individuals 16 years of age or older may consent to an abortion on their own behalf; for purposes of abortion services, a minor is considered to be an individual under the age of 16 (19a-600)
- iii. Individuals 17 years of age have the legal capacity to consent to donation of blood or any component thereof and to the withdrawal of blood in conjunction with any voluntary blood donation program (19a-285a).

3) A minor may legally consent to medical, dental, health, and hospital services for his or her child (19a-285)

To the extent that Connecticut law does not require parental consent, but also does not specifically grant the child the legal capacity to consent to research (i.e. the types of care described in section 5.2 above), the Connecticut Children's 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 Legal Department as needed. NOTE: For research conducted in jurisdictions other than Connecticut, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The Legal Department will provide assistance with regard to the laws in other jurisdictions as needed.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Connecticut a "Guardian" of a minor has the duty and authority to act in the best interests of the minor, and this includes the obligation of care and control, and the authority to make major decisions affecting the minor's education, welfare, and major medical decisions (C.G.S 45a-604(5)).

NOTE: For research conducted in jurisdictions other than Connecticut, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The Legal Department will provide assistance with regard to the laws in other jurisdictions as needed.

Legally Authorized Representative (LAR). A legally authorized representative is 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 legally authorized representative for children includes a parent or court-appointed legal guardian. For subjects 18 years of age or older, a legally authorized representative includes a court-appointed legal guardian or conservator, a person appointed as a health care representative in accordance with C.G.S 19a-570(5), or a person designated as having a power of attorney for health care. In almost all cases at Connecticut Children's, the research involves children and the parent (or other legal guardian) is the LAR.

Parent means a child's biological or adoptive parent.

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

5.3 Basic Requirements

Investigators must obtain informed consent/parental permission prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent/parental permission from a subject or legally authorized representative, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

Note: These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

5.4 Research with Children

It is an established ethical and legal precept that subjects may only be included in research studies if they have given their informed consent to participate. Informed consent requires that potential subjects comprehend the relevant specific information about the research, including its risks and potential benefits, and that they make a free and informed decision to participate, without coercion.

Inclusion of children as participants in research studies, therefore, presents unique and important legal and ethical challenges. Very young or very sick children, especially, may be unable to comprehend the complexities of agreeing to participate in a research

study. Even an older child whose comprehension and judgment may approach that of an adult still lacks the legal authority to make binding decisions regarding his or her own care (with the limited exceptions of several statutory provisions, noted in Section 5.2, above). Therefore, informed consent in the context of research with children shifts away from the model of a competent adult who provides informed consent, and becomes instead a model in which parents (or other legal guardians) provide permission for their child to participate in a research study, and the child assents to participate, to the extent possible and when required. References in this Manual to “informed consent” can be understood to incorporate parental permission, as appropriate. Specific requirements regarding parental permission and assent are outlined in greater detail below.

Federal law affords special protections to children participating in research. When reviewing research involving children, the IRB must include one or more individuals who are knowledgeable about or experienced in working with children. In addition, when reviewing research with children, the IRB must make specific risk/benefit and assent are outlined in greater detail below.

5.5 Informed Consent/Parental Permission Process

Informed consent/parental permission is not merely a signature on a form or disclosure of information, but an interactive process of mutual communication. The process starts before any form is signed and continues throughout the entire study. The process begins by meeting with prospective subjects and their families and discussing the research. In pediatrics, the decision to participate in research should be a family-centered decision with special consideration and attention given to each parent/guardian and the pertinent child or adolescent. In some situations it may be appropriate to spend time with the child/adolescent alone, without the parent/guardian present. This may make it easier for the child to ask questions and not feel coerced by a parent/guardian. Investigators should consider the best method for obtaining consent/permission and assent, and to be mindful of factors such as nature, location, and urgency of the research, as well as family dynamics. Investigators are encouraged to consider innovative and creative ways to provide children and families with information about the study during the informed consent process (for example, use of videotapes or photographs of research procedures, pre-visits to the site of the research to see equipment, such as MRIs, comics or cartoons explaining aspects of the research, arranging to speak with current or former participants, etc.).

The written consent form is a formalization of the agreement to participate, and it is used to document a process. Investigators must explain the research in terms that both the children and the parents/guardians can understand. Subjects and families must be able to describe what they are consenting to do. Investigators or other study personnel engaged in the consenting/permission process should consider what open-ended questions would help ascertain parents’ and potential subjects’ comprehension

(for example, "Could you explain to me what we are going to ask you to do in this study?", or "Can you tell me the possible good and bad things that may happen if you take the experimental drug?")

Because informed consent continues throughout the entire research activity, subjects and their families must be kept apprised of new information regarding the study. They must have the opportunity to ask, and be encouraged to ask, ongoing questions. Subjects and families may be kept up-to-date through verbal discussions, written materials, and, when necessary, by having a subject re-sign a written informed consent document that contains additional information. It is important to keep in mind that subjects/families retain the right to withdraw at any time, and to remind them of that fact.

Informed consent/parental permission must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent.
2. The informed consent/parental permission process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to discuss and consider whether or not to participate.
3. The informed consent/parental permission process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
4. The informed consent/parental permission information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to the 8th grade level, using lay terms where possible in the description of the research.
5. For subjects whose native language is not English, informed consent/parental permission must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent/parental permission processes include a reliable translator/interpreter when the prospective subject does not understand the language of the person who is obtaining consent. To avoid placing undue pressure on family members, it is Connecticut Children's IRB policy that family members should not serve as translators/interpreters.
6. The informed consent/parental permission process may not include any exculpatory language through which the subject or legally authorized representative is made to waive, or appear to waive, any of the subject's legal rights; or through which the investigator, the sponsor, Connecticut Children's or Connecticut Children's employees or agents are released from liability for negligence, or appear to be so released.
7. The PI is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the

information provided.

Note: Connecticut Children's does not utilize the provisions for broad consent.

5.6 Elements of Informed Consent/Parental Permission

While the applicable regulatory criteria for consent will be used as the general premise for all consent forms, when the research is not federally funded or supported, nor subject to FDA oversight, the IRB may exercise judgement as to whether the elements noted below are required. In all cases, the consent form must provide sufficient detail for the potential subject to make an informed decision.

The following table presents the required elements of consent/parental permission for federally funded or supported (FFS) research and the requirements for FDA regulated research.

Elements noted with an (+) are the newly added elements from the 2018 revision of 45 CFR 46. These elements will be required for:

- FFS research initially approved after the effective date of the regulation
- FFS research approved prior to the effective date of the revised rule which is continuing to enroll participants and that is being transitioned to review under the revised regulations

Unless consent has been completely waived, elements noted with * cannot be omitted or altered for FFS research approved in accordance with the revised regulation.

FDA	FFS	Element
	X	The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information. ⁺ *
	X	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. ⁺ *
	X	Informed consent as a whole 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. ⁺ *
X	X	A statement that the study involves research
X	X	An explanation of the purposes of the research
X	X	Expected duration of the subject's participation
X	X	A description of the procedures to be followed
X	X	Identification of any procedures that are experimental
X	X	A description of any reasonably foreseeable risks or discomforts to the subject
X	X	A description of any benefits to the subject or to others which may reasonably be expected from the research
X	X	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

X	X	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
X		For studies involving the use of drugs, devices, or biologics, a statement that indicates that the FDA and sponsor may inspect the records
X	X	For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of research-related injury , including who will pay for the treatment and whether other financial compensation is available
X	X	An explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject
X	X	Contact information for the IRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant, in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff
X	X	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
	X	One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: • 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 if this might be a possibility; or • a statement that the subjects information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
X	X	Unless waived, a signature line for the subject in addition to the IRB-required date line for the subject
As applicable		
X	X	For applicable clinical trials subject to FDA regulation and/or funded by NIH the following required statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov , as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time."
X	X	A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
X	X	A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.

X	X	Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
X	X	Any additional costs to the subject that may result from participation in the research. (For example: Include when it is anticipated that subjects may have additional costs.)
X	X	The consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences).
X	X	Procedures for orderly termination of participation by the subject. (For example: include when the protocol describes such procedures.)
X	X	A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
X	X	The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)
	X	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 ⁺
	X	A statement regarding whether clinically relevant research results, including the individual research results, will be disclosed to subjects, and if so, under what conditions ⁺
	X	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) ⁺
		Any conflict of interest disclosure. This should be included in any protocol that the IRB determines it is necessary to disclose to subjects a real or potential COI for the investigator or institution.
		Other disclosures that might be relevant to a particular study (e.g., risk of determining unreported sexual abuse, neglect or suicidality; requirement for pregnancy testing, etc.)
		The amount and schedule of payments
		If participants will receive \$600 or more within a calendar year: You are responsible for paying any state, federal, or other taxes on payments you receive. Since Connecticut Children's Medical Center may be required to report the amount of payment you receive to the Internal Revenue Service (IRS), you will be asked to complete a W-9 form in order to receive payment.

		If participants will be receiving financial compensation (not reimbursement) by check, the consent form must state that Connecticut Children's will collect a W-9 from the participant.
		If study involves genetic testing: A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: 1. Health insurance companies and group health plans may not request your genetic information that we get from this research. [Note that if an insurance company or health plan administrator is engaged in the research in accordance with the requirements of the research exception, this bullet should be modified accordingly.] 2. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. 3. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

5.7 Allowable Categories for Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

5.7.1 Allowable Categories

The IRB may only approve research on children if it satisfies one of the following categories. The IRB documents and determines the allowable category the research is approvable under when research involves children:

1. Research not involving risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**).

- Adequate provisions must be made for soliciting the assent of children (when in the judgment of the IRB the children are capable of assenting) and for obtaining the permission of their parents or guardians (see Section 5.7.1.1, Parental Permission).
 - For research subject to EPA requirements, the IRB can utilize this category for observational research not involving greater than minimal risk. Observational research is defined as research with human subjects that does not meet the definition of research involving intentional exposure of a human subject.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. For this finding:
- The risk must be 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 children (when in the judgment of the IRB the children are capable of assenting) and for Parental Permission)
 - **Note:** assent is not required if 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 children and is available only in the context of the research.
 - For research subject to EPA requirements, the IRB can utilize this category for observational research involving greater than minimal risk with the prospect of direct benefit only if all of the above criteria have been met.
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. In addition:
- 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 subject's 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 the assent of children (when in the judgment of the IRB the children are capable of assenting) and obtaining the permission of their parents or guardians (see Section 5.7.1.1, Parental Permission).
 - **Note:** Permission of both parents, or legal guardian, is required,

unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child;

- For research subject to EPA requirements, this category cannot be utilized.

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

- HHS-conducted or funded research in this category must be approved by the Secretary of Health and Human Services for HHS-funded or supported research
- FDA-regulated research in this category must be approved by the Commissioner of Food and Drugs.
- For research subject to EPA requirements, this category cannot be utilized.

5.7.1.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 5.6.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 & 2 above. The IRB's determination of whether consent must be obtained from both parents will be documented in the consent checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent/permission from both parents is required for research to be conducted under Categories 3 & 4 above unless

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. Only one parent has legal responsibility for the care and custody of the child.

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

- The research meets the provisions for waiver in Section 5.11, 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.

Note: Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Sections 5.5 and 5.9.

5.7.2 Assent from Children

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.

The IRB should 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. Therefore, the IRB determines if assent is a requirement of all children, some children, or none of the children. 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.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a “no” from the child overrides a “yes” from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the research holds out the prospect of a direct benefit that is only available through participation in the research, in which case a

parent's decision may override a child's refusal to assent). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that 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 children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this manual.

5.7.3 The Assent Form

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. tell why the research is being conducted;
2. describe what will happen and for how long or how often;
3. say it's up to the child to participate and that it's okay to say no;
4. explain if it will hurt and if so for how long and how often;
5. say what the child's other choices are;
6. describe any good things that might happen;
7. say whether there is any compensation for participating; and
8. ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations or cartoons might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language. If the study includes children from a broad age range, it may be appropriate to have a simpler assent form for younger participants and a more detailed one for older adolescents.

5.8 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in 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:**

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, 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*.

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.

5.9 Documentation of Informed Consent

Except as provided in Section 5.12 of this document, informed consent/parental permission must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) and dated by the subject or the subject's legally authorized representative at the time of consent.
2. A copy of the signed and dated consent form must be given to the person signing the informed consent form.
3. The informed consent form may be either of the following:
 - a. A written informed consent form that meets the basic and required additional elements of informed consent (as outlined in sections 5.3, 5.5, and 5.6 above). The investigator must give the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed and prior to participating; alternatively, this form may be read to the subject or the subject's legally authorized representative.
 - b. A short form written informed consent form stating that the elements of informed consent have been presented orally to the subject (or the subject's legally authorized representative); for federally-supported research, the key information must be presented first to the subject, before other information. If the nature of the research suggests that a significant number of non-English speaking subjects will be enrolled, the IRB will require the PI to obtain a translated consent form. When the PI unexpectedly encounters a subject who does not read or is not fluent in English, the following short form method may be used:

- i. The IRB must approve a written summary that embodies the basic and required additional elements of disclosure (the English language consent form approved by the IRB may serve as the summary);
- ii. There must be an interpreter present who is fluent in both English and the preferred language of the participant. When the investigator presents the consent information to the participant, the interpreter presents the information in the participant's preferred language, and facilitates dialogue between the research team member obtaining consent and the participant. The following individuals are authorized to serve as an interpreter in compliance with the institutional Communication and Language Services" policy.:
 - Connecticut Children's Child & Family Language Services
 - A bilingual member of the study team
 - Other bilingual Connecticut Children's employee (non-research personnel)
 - Over the Phone or Video Remote interpreting service

Connecticut Children's has an institutional policy "Communication and Language Services" which outlines basic, moderate, and complex interpretations; the process for arranging services, guidance on what documents require written translation, and documenting the use of interpreters or translators. In the research setting, the IRB will determine the appropriateness of the individual(s) proposed to interpret/translate based on guidance set forth in the policy.

- iii. There must be a witness to the oral presentation. If the participant does not speak English, the witness will be conversant in both English and the language of the participant, and is not part of the study team or otherwise involved with the study. The following individuals are authorized to serve as a witness:
 - The translator/interpreter may serve as the witness.
 - Other bilingual Connecticut Children's employee
 - An adult family member who is not the Guardian/Legal Authorized Representative (LAR)
- iv. At the conclusion of the consent discussion, the subject is to be asked if they understood the information in the summary document that was verbally presented to them in their preferred language, as well as any additional information conveyed by the person obtaining consent (including responses to the subject's questions) and the participant must respond affirmatively.
- v. Required Signatures:
 - The participant (or legally authorized representative) must sign

- and date the short form consent document;
 - The witness must sign both the short form and a copy of the summary;
 - The research personnel/study team member actually obtaining consent must sign a copy of the summary;
 - vi. A copy of the summary must be given to the subject or representative, in addition to a copy of the signed short form; and
 - vii. At the time of continuing review, the PI should notify the IRB if any subjects have been enrolled using the short form consent process.
4. When determining whether to allow the use of the short form, the IRB shall determine if the research involves the short form method described above.

5.10 Consent Monitoring

In reviewing the adequacy of informed consent/parental permission procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that subjects are truly giving informed consent. Such monitoring may be particularly warranted for:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving highly vulnerable populations (e.g., ICU patients or terminally ill patients)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or
- Other situations when the IRB has concerns about the consent process

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Chair may consult with the HRPP Medical Director and/or Director to develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately completed and documented,

- Whether the participant had sufficient time to consider study participation,
- Whether the consent process involved coercion or undue influence,
- Whether the information was accurate and conveyed in understandable language, and
- Whether the subject appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

5.11 Waiver of Informed Consent

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above; or waive the requirements to obtain informed consent/parental permission, provided the IRB finds and documents that:

- (a) The research/clinical investigation involves no more than minimal tangible or intangible risk to the subjects;
- (b) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (c) The research/clinical investigation could not practicably be carried out without the waiver or alteration;
- (d) If the research/clinical investigation 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; and
- (d) Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

When granting an alteration to the required elements of informed consent, for federally-supported research, the following elements cannot be omitted or altered:

- Before involving a human subject in research an investigator shall obtain the legally effective informed consent of the subject.
- Informed consent will be sought only under circumstances that provide the prospective subject sufficient opportunity to discuss and consider participation and that minimize the possibility of coercion or undue influence.
- The information that is given to the subject shall be in a language understandable to the subject
- Exculpatory language which releases or appears to release the institution, sponsor or investigator from liability or which makes or appears to make a subject waive any legal rights cannot be included in the ICF

- The prospective subject must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information
- Informed consent as a whole 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 understanding of the reasons why one might or might not want to participate
- The informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject 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

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent/parental permission, provided the IRB finds and documents that:

(a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

1. Public benefit or service programs
2. Procedures for obtaining benefits or services under those programs
3. Possible changes in or alternatives to those programs or procedures; or
4. Possible changes in methods or levels of payment for benefits or services under those programs.

(b) The research could not practicably be carried out without the waiver or alteration.

Screening, recruitment, or determining eligibility

The IRB can approve a research study in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining eligibility of prospective subjects without the informed consent of the prospective subject if either of the following conditions are met:

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

5.12 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

1. The only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality; **or**
[**Note 1:** Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)
Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.
Note 3: The oral or written information provided to participants includes all required and appropriate additional elements of consent disclosure.]
2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.
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.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

5.13 Subject Withdrawals from Clinical Trials

When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the participant the option of having data removed. A researcher may ask a participant who decides to withdraw to provide continued follow-up and further data collection subsequent to the subject's withdrawal from the interventional portion of the study. During the discussion, the researcher distinguishes between the study-related intervention and continued follow-up of associated clinical outcomes information (e.g., laboratory results or medical course obtained from chart review). During the discussion with the subject, the researcher also discusses the privacy and confidentiality of the participant's information.

The researcher must obtain consent for the participant's limited participation in the research unless the original consent document addressed this situation.

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

5.14 Posting of Clinical Trial Consent Forms

For each federally funded or supported clinical trial, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee of the Federal department or agency component conducting the trial on a publicly available Federal website that acts as a repository for such informed consent forms. The informed consent form must be posted after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol. Principal investigators are responsible for working with the funding agency to address this requirement.

6 Additional Protections for Subject Populations in Research

6.1 Policy

When some or all of the participants in research conducted under the auspices of Connecticut Children's are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. In addition to children, there are additional protections for research involving pregnant women, fetuses, neonates, prisoners, or adults who lack the ability to consent. The IRB must ensure that all of the regulatory requirements for the protection of these subjects are met.

6.2 Definitions

Delivery means complete separation of the fetus from the woman by expulsion, extraction, or any other means.

Fetus is the product of conception from the time of implantation until delivery.

Viable fetus is now termed a "viable neonate."

Nonviable fetus is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining heart and respiration, even given the benefit of available medical therapy. ***NOTE: In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.***

Dead fetus is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

In vitro fertilization is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

Neonate means newborn.

Viable neonate means being able, after delivery, to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).

Non-viable neonate means the same as a non-viable fetus.

Pregnancy is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

Prisoner is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Surrogate Consent is consent obtained from a legally authorized representative on behalf of a participant determined to lack decision-making capacity.

6.3 Involvement of Subject Populations

If the IRB reviews research that involves categories of participants, including children, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. For example, the IRB will include one or more individuals who are knowledgeable about or experienced in working with prisoners, or adults with limited decision-making capacity, if reviewing research that involves individuals from these populations. When research is likely to involve participants likely to be vulnerable to coercion or undue influence, the IRB chair will ensure that at least one IRB member knowledgeable about or experienced in working with such participants is present at the meeting.

45 CFR 46 includes subparts designed to provide extra protections for these populations which also specify additional requirements for IRBs:

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research*
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional Protections for Children Involved as Subjects in Research (discussed above in section 5)

*It should be noted that Subpart B pertains to *non-viable* neonates or neonates of *uncertain viability*. “Viable” neonates are considered “children” and would be covered in Subpart D protections.

DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

Note: the subparts only apply to federally-supported research (FDA regulations also include Subpart D (regarding children), which applies to all FDA-regulated research). The following policies and procedures, which are based on the subparts, apply to all research regardless of funding. The individual sections describe how the subparts apply to federally supported research.

6.4 Responsibilities

1. The PI is responsible for identifying the potential for enrolling these subject populations in the research proposal. The PI is responsible for identifying patients who are at risk for impaired decisional capacity as a consequence of psychiatric illness, and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or ad hoc consultants, of individual(s) interested in or who have experience with the populations involved in a research proposal.
3. The IRB reviews the PI's justifications for including these populations in the research to assess appropriateness of the research proposal.
4. The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of subjects as needed at the time of initial review of the research proposal.
5. The IRB shall continue to review research at intervals appropriate to the degree of risk and determine whether the proposed research continues to fulfill criteria for approval. Information reviewed should include the number of participants considered as members of specific vulnerable populations.
6. For studies that do not have or are not required to have a Data and Safety

Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable subjects, the IRB needs to carefully review the data and safety monitoring plan.

7. The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

6.5 Procedures

Initial Review of Research Proposal:

1. The PI should identify the potential to enroll these subject populations in the proposed research at initial review and provide the justification for their inclusion in the study.
2. The IRB evaluates the proposed plan for consent of the specific populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a data and safety monitoring board or data monitoring committee as appropriate.
5. The PI should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
 - a. Examples of studies that warrant consideration of independent monitoring include those involving schizophrenic patients who will be exposed to placebo, and/or drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations requiring independent monitoring would include individuals with schizophrenia, other psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders.
6. The IRB assesses the adequacy of additional protections provided by the PI.

6.6 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research regardless of funding source.

6.6.1 Research Involving Pregnant Women or Fetuses

6.6.1.1 Research Not Federally Supported

For research not federally supported, no additional safeguards are required and there

are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal.

Pregnant women or fetuses may be involved in research not federally funded involving more than minimal risk to fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, or the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 5;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.6.1.2 Research Federally-Supported

For federally supported research, 45 CFR Subpart B applies to all research involving pregnant women. Under 45 CFR Subpart B, pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph (4) or (5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 5;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

*In addition to the above noted requirements in section 6.6.1.2, additional requirements apply to Environmental Protections Agency supported research, as outlined in the applicable Appendix of this document.

6.6.2 Research involving neonates

If consent is obtained under paragraph (4) or (5) of the above sections 6.6.1.1 or 6.6.1.2 during pregnancy, and additional research with the neonate will continue following delivery, re-consent is not required so long as the consent form adequately describes all procedures to occur post delivery, including any follow up with the infant or child, and the IRB makes the appropriate determinations for consent in research involving neonates as described below. The consent form should clearly reflect that the pregnant woman is providing consent both on her own behalf under Subpart B and as the prospective parent/guardian of the child to be born under Subpart D. If the IRB determines that additional parental consent is required under subpart D as described in the section "Research involving Children", then re-consent is required upon birth of the child.

Similarly, if HIPAA authorization is obtained during pregnancy and additional research will continue following delivery, HIPAA re-authorization is not required so long as the HIPAA form adequately describes all health related information used or disclosed in connection with the neonate following delivery, including information that may

originate from the mother's own medical records but pertains to the neonate's health.

Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met: The IRB determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.
6. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except

that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

Viable Neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of IRB Review Process and Research Involving Children.

6.6.3 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
2. If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of this manual are applicable.

6.6.4 Research Not Otherwise Approvable

HHS-conducted or funded research that falls in this category must be approved by the Secretary of Health and Human Services. 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 pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review and approval by the Secretary of Health and Human Services.

6.7 Research Involving Prisoners

In the event that a research study is proposed that will involve prisoners or a participant in a research study becomes a prisoner, the HRPP will utilize the applicable Appendix of this document to guide the review process.

6.8 Adult Subjects with Impaired Decision-making Capacity

Very rarely, a situation may arise in which a Connecticut Children's investigator provides care for and might wish to offer research participation to adults whose unusual condition, or history of continuous treatment or relationship with a specific Connecticut Children's program or physician, provides a compelling reason to allow them to continue to be treated at Connecticut Children's.

The requirements in this section apply to these rare circumstances, regardless of funding source, where an investigator seeks permission to include an adult subject with impaired decision making capacity. Investigators are encouraged to seek guidance in advance from the IRB/HRPP Office regarding requirements for inclusion of such subjects in research studies. The IRB/HRPP Office will seek advice from the Legal Department as needed.

Persons with intellectual disabilities who have been declared incompetent by court: Under Connecticut law, persons with intellectual disabilities who have been declared incompetent to make medical decisions and appointed a legal guardian to do so on their behalf must have their appointed legal guardian provide consent to participate in research. A legal guardian with the authority to consent to health care treatment may consent to participation in an experimental procedure or biomedical or behavioral experiment if one of the following criteria is met:

1. intended to preserve life or prevent serious impairment of physical health (CGS 45a-677(e).); OR
2. intended to assist a ward in any way in regaining abilities and has been approved for the ward by the court; (C.G.S. 45a-677(e)); OR
3. has been (i) approved by a recognized institutional review board, as defined by 45 CFR 46, 21 CFR 50 and 21 CFR 56, as amended from time to time, which is not a part of the Department of Developmental Services, (ii) endorsed or supported by the Department of Developmental Services, **and** (iii) approved by the ward's primary care physician (C.G.S. 45a-677(e)).

For the 3rd criterion, the preferred process for obtaining endorsement/support from the Department of Developmental Services (DDS) is for the guardian to send a letter to DSS describing the study and anticipated benefits, along with approval from the primary care physician, to request DSS' endorsement. However, this could also be done by the Connecticut Children's research team if needed (ie for some reason the guardian was not being responsive or having trouble navigating the process). Then, DSS would provide a letter indicating its endorsement/support.

** Note that not all research will be considered "experimental" in nature. Many types of research (e.g. records review, other research not involving a direct treatment/procedure or where the treatment being applied is considered routine). In these cases, the limitations above would not apply and the guardian may consent as part of their authority to consent to routine health care/records release.*

When research involves an adult subject that has impaired decision-making capability but has not been declared incompetent by the court and/or the research activities are not considered experimental in nature: one of the following conditions must apply:

1. Only incompetent persons or persons with impaired decision making capacity are

suitable as research subjects because the research pertains to the individual's disability or impairment. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a significant risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

When research involving adult subjects with impaired decision-making capability is planned, the procedures below must be followed:

- The natural parents of the adult are not authorized to give permission unless they have been appointed legal guardian(s) for the purposes of consenting to health care treatment. If a person with an intellectual disability has not been declared incompetent, the PI must decide if the subject is capable of understanding the elements of informed consent and a family member or other representative may be asked to co-sign. If the investigator determines the subject is not capable of providing consent, a legal guardian must be appointed and must provide consent before the subject can be enrolled.
- Procedures have been devised to ensure that participants' representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Court-appointed guardians or conservators (or, when applicable, health care representatives) must be given descriptions of both the proposed research study and the obligations of the person's representatives. They must be reminded that their obligation is to try to determine what they think is in the incompetent person's best interest (or in the case of a conservator, to act in accordance with the conserved person's preferences to the extent these can be determined and would not cause substantial harm).

6.8.1 IRB composition

The IRB membership must include at least one member who is an expert in the area of the research. Consideration may be given to appointing another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population. The IRB may solicit the expertise of consultants as necessary to ensure appropriate scientific expertise (consultants may not vote).

6.8.2 Determination of Decision-Making Capacity

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the adult subject may not be capable of making voluntary and informed decisions about research participation. The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate.

For research protocols that involve adult subjects with cognitive, developmental, or psychiatric disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with cognitive, developmental, or psychiatric disorders.

For research protocols involving adult subjects who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

In the event adult research participants become incompetent or impaired in decision

making capacity after enrollment, the PI is responsible for notifying the IRB office. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research participants.

6.8.2.1 Determining Capacity to Consent

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

- Ability to evidence a choice,
- Ability to understand relevant information,
- Ability to appreciate the situation and its likely consequences, and
- Ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

For studies that have been approved for enrolling vulnerable adult populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential subject to consent. The PI may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. Additionally, if the reason for lack of capacity is because of mental illness then a psychiatrist or licensed psychologist must confirm this judgment and document in the individual's medical record in a signed and dated progress note.

An adult person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. Should the person object to participating, this objection should be heeded.

6.8.3 Informed Consent and Assent

Whenever the adult participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and documented in accordance with Section 5 above. When adult participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent) as described below.

An adult person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate

assent form. If the person objects to participating, this objection should be heeded.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For adult subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

6.8.4 Surrogate Consent (Adult Subjects)

The regulations generally require that the investigator obtain informed consent from subjects. Under appropriate conditions, investigators also may obtain informed consent from a *legally authorized representative* of a subject (surrogate consent).

Definition: *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [45 CFR 46.102(c)].

This policy is designed to protect human subjects from exploitation and harm.

Surrogate consent for an adult subject may be obtained from a court appointed guardian or conservator with authority to consent to health care treatment; a health care representative appointed by the person; or by an individual designated as having an appointed health care representative (e.g., a previously competent subject might have designated an individual to provide consent with regard to health care decisions through an appointment of a health care representative and have specified that the individual also has the power to make decisions on entry into research.) Permission from next-of-kin is not acceptable absent one of the prior designations.

In addition to a court-appointed legal guardian, the following are other types of legally authorized representatives for adults

- **Conservator** - Adults who do not meet the statutory criteria for an intellectual disability, but may have some level of impaired decision-making capacity, may have an appointed conservator (rather than a guardian), who may have the authority to make medical decisions. A conservator must promote the conserved person's preferences and actively encourage the conserved person to participate in decisions, and is expected to make decisions based on the conserved person's preferences as opposed to the conservator's view of what is in the best interests of the conserved person unless the conservator cannot determine the preference or the preference could cause substantial harm. Depending on the nature of the research, the conservator may need or want to seek court approval prior to consenting.
- **Health Care Representative** - Likewise, an adult who was once competent but is no

longer competent may have appointed a “health care representative” to make decisions in the event of their future incapacity.

In order to document that the guardian can provide consent for research, documentation must include:

- Adult with plenary or limited guardian:
 - o Copy of current court order naming the legally authorized representative as either:
 - Plenary guardian
 - Limited guardian with power to consent to release of clinical records and/or medical treatment, as applicable
 - o AND, if applicable, evidence of DDS/Probate Court approval unless exception applies
- Conservator:
 - o Current court order naming the individual as conservator and including the ability to consent to medical care
 - o Court order authorizing participation (if sought by conservator)
- Health care representative:
 - o Appointment of Health Care Representative signed by represented individual

6.8.5 Children who Begin Research as Children and Become Adults who are Decisionally Impaired During the Course of the Study

If a child turns 18 during the course of a study, and the study involves continuing diagnostic/therapeutic procedures, or any form of research intervention, informed consent must be obtained from the now adult in order to remain in the research. If the now adult subject is decisionally impaired, the investigator is required to consider and follow the consent policies set forth above. Parents do not automatically maintain the ability to consent for the now adult study subject unless they have been appointed by the court as the subject’s legal guardian. If there is no court appointed guardian, the same policies for legally authorized representatives set forth above apply. A new consent document would need to be signed with the appropriate legally authorized representative, regardless of whether it is the same person that signed the consent form originally.

6.8.6 Involvement of a Decisionally Impaired Adult in a Protocol where the IRB has not Considered the Above Referenced Special Protections

An investigator may wish to enroll a decisionally-impaired adult subject in a protocol when it was not anticipated that decisionally-impaired subjects would be enrolled. In this situation, the investigator and IRB have not had the opportunity to consider the special protections listed above and consider the arrangements necessary for the informed

consent process. In these circumstances, the investigator must contact the IRB Office to discuss the situation and consider any necessary arrangements in order to include the subject in the research. The issues and principles listed above will be considered in determining whether it is appropriate to include the subject in the research.

7 Investigational Drugs & Devices

7.1 Policy

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the use of investigational drugs and devices in research under the auspices of Connecticut Children's.

7.2 Definitions

Investigational Drug. The term drug means:

- (A) Articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia, or official National Formulary, or any supplement to any of them; and
- (B) Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- (D) Articles intended for use as a component of any article specified in clause (A), (B), or (C).

When food & dietary supplements are used to study the diagnosis, cure, mitigation, treatment, or prevention of *disease* in man or other animals; they are drugs.

"A medical food is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Medical foods are not drugs and, therefore, are not subject to any regulatory requirements that specifically apply to drugs. (Orphan Drug Act (21 U.S.C. 360ee (b) (3))

Investigational Device. The term device means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article including any component, part, or accessory, which is –

- (1) Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them
- (2) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or other animals, or

Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

Emergency Use. Emergency use is defined as the use of an investigational drug, biologic, or device with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and:

- (a) For use of drugs/biologics, there is not sufficient time to obtain IRB approval.
- (b) For use of devices, there is not sufficient time to obtain FDA authorization

Significant Risk (SR). Significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk (NSR). A non-significant risk device is an investigational device other than a significant risk device.

Humanitarian Use Device (HUD). Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year.

7.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

7.4 IND/IDE Requirements

The PI must indicate on the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

1. Sponsor protocol imprinted with the IND/IDE number
2. Written communication from the sponsor documenting the IND/IDE number
3. Written communication from the FDA documenting the IND/IDE number

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

When research is conducted to determine the safety or effectiveness of a device, the Human Research Protection Program Director or an HRPP/IRB staff designated by the HRPP Director confirms that the device fulfills the requirements for an abbreviated IDE.

1. The device is not a banned by the FDA.

2. The sponsor labels the device in accordance with 21 CFR 812.5.
3. The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval.
4. The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived.
5. The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
6. The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
7. The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
8. The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

7.4.1 IND Exemption

For drugs, an IND is not necessary if all seven of the following conditions are met:

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Note: The following are also exempt from the IND requirements: (a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and (b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

1. It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
2. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
3. It is shipped in compliance with 312.160

7.4.2 Exempted IDE Investigations

For devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device – other than a transitional device, introduced into commercial distribution on or after May 28, 1976 -- that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,
 - c. Does not by design or intention introduce energy into a subject, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

7.5 Responsibilities

7.5.1 PI

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and Connecticut Children's policies and procedures
2. The PI must obtain approval from the IRB before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the drug/biologics/device.
4. The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. The PI will delegate the responsibility for drugs/biologics accountability to the Pharmacy Service.
5. All investigational drugs will be stored under appropriate security when and to the extent applicable and dispensed by an authorized dispenser/individual.
6. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
7. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 8.
8. For research involving investigational new drugs:
 - a. The PI is required to inform Pharmacy Service that IRB have approved the protocol through submission of the IRB approval letters (IRBManager may automatically provide notification and access to approval letters to Pharmacy Service, but the responsibility is ultimately that of the PI).
 - b. The PI must inform the IRB and Pharmacy Service when a study involving investigational drugs has been terminated by the sponsor.
 - c. The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
 - d. The PI will maintain the following:
 - i. Current curriculum vitae (CV)
 - ii. Protocol
 - iii. Records of receipt and disposition of drugs
 - iv. List of any co-investigators with their curriculum vitae
 - v. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and
 - vi. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the

investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to Pharmacy Service and the IRB in the manner defined by the protocol.

- vii. IRB letters of approval.
- viii. Other documents as may be required by this HRPP Manual

9. For research involving investigational devices:

- a. If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
- b. If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining.
- c. The PI will maintain the following:
 - i. Current curriculum vitae (CV)
 - ii. Protocol of the study
 - iii. Records of animal study reports
 - iv. Records of receipt and disposition of devices
 - v. List of any co-investigators with their curriculum vitae
 - vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation
 - vii. Case histories with particular documentation on evidence of effects.
 - viii. Emphasis is on safety and possible untoward happenings. All adverse device effects are reportable
 - ix. IRB letters of approval and the EOC Committee approval letter if applicable.
 - x. Device training.
 - xi. Other documents as required by this HRPP Manual.
- d. Following completion of the study the termination procedure for investigational drugs must be applied if pharmacy control, or if the devices are kept by the investigator the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.
- e. If, after use, the PI keeps the devices, he/she must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

- f. Investigators must report possible unanticipated problems to the sponsor and the IRB as soon as possible, and no later than within five (5) working days of receiving notice of the event, if the event requires immediate intervention to prevent serious harm to participants or others. Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the sponsor and the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. PIs who act as sponsors must review the relevant Guidance Documents on Requirements of the Sponsor and the Investigator as a Sponsor, and must comply with the regulatory responsibilities of a sponsor. The HRPP Office and/or the Research Compliance Manager will conduct education sessions as needed for investigators holding an IND or IDE on the sponsor regulations, and may periodically conduct or request that the Research Compliance Manager conduct random reviews of PIs holding an IND or IDE.

7.5.2 IRB

1. The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
2. For research involving the use of a drug, the IRB will confirm that the drug has an IND or the research meets one of the FDA exemptions from the requirement to have an IND.
3. For research involving investigational devices, the IRB will confirm that the device has an IDE issued by the FDA, the device fulfills the requirements for an abbreviated IDE, or the research meets one of the FDA exemptions from the requirement to have an IDE. The IRB will make a determination whether the device is a significant or non-significant risk device unless the device has an IDE issued by the FDA, the research meets one of the FDA exemption from the requirements to have an IDE, or the FDA has already made a risk determination for the study. The IRB's process for making a significant or non-significant risk determination is described below:
 - a. The IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated

requirements of IDE regulations. If the study that has been submitted as NSR is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

- b. The IRB will not review protocols involving significant risk devices under expedited review.
- c. The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.
- d. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

7.6 Emergency Use

7.6.1 Emergency Exemption from Prospective IRB Approval.

HHS regulations do not permit human subjects research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. Furthermore, the data obtained from the patient may not be classified as human participant research and the outcome of emergency care cannot be included in any report of a research activity subject to DHHS regulations. However, nothing in the HHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State or local law.

FDA defines emergency use as the use of an investigational drug, biologic, or device with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which: for use of drugs/biologics, there is not sufficient time to obtain IRB approval or for use of devices, there is not sufficient time to obtain FDA authorization. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Under FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application.

This notification must not be construed as an approval for the emergency use by the IRB. The HRPP Medical Director or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations.

7.6.2 Emergency Use of a Drug or Biologic

Investigator Responsibilities

1. An investigator who is a licensed physician must confirm that the disease is serious or immediately life-threatening, that there are generally no acceptable alternatives for the treatment, and that there is not sufficient time for the IRB to review and approve the investigational use.

2. Obtain an IND from the FDA as required under 21 CFR 312.310;

If the use of the unapproved test article does not meet the criteria of an existing study protocol or if an approved study protocol does not exist, the treating physician must contact the manufacturer of the test article and determine if it can be made available for emergency use under the manufacturer's IND.

If the manufacturer is unwilling to sponsor the emergency use through its IND, and there is no time for the investigator to submit an IND, the investigator must obtain the FDA's authorization and the manufacturer's agreement to ship the unapproved test article.

3. Obtain and document informed consent from the subject or the subject's legal representative unless the circumstances meet the exception under FDA regulations at 21 CFR 50.23 which permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- The subject is confronted by a life-threatening situation necessitating the use of the test article;
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- Time is not sufficient to obtain consent from the subject's legally authorized representative;
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

4. After emergency use:

- i. The IRB must be notified within 5 working days. The HRPP Medical Director/IRB Chair or designee will review the report to verify that circumstances of the emergency use conformed to FDA regulations.
- ii. If an unanticipated problem involving risk to subjects or others (e.g., an SAE that was unexpected and related) occurred in connection with the emergency use, submit reports consistent with the reporting requirements of the IRB, the FDA, and the manufacturer of the test article.

- iii. If the manufacturer agreed to sponsor the emergency use through its IND, provide the manufacturer with a written summary of the conditions constituting the emergency, subject protection measures, and the results of the emergency use. In these cases, the manufacturer is responsible for corresponding with the FDA
 - 1. If the manufacturer did not agree to sponsor the emergency use through its IND, the treating physician must provide the FDA and the manufacturer with a written summary of the conditions constituting the emergency, subject protection measures, and the results of the emergency use within a formal IND application within 15 business days and:
- iv. Submit annual reports
- v. If there is no plan for submission of a formal protocol for additional uses, submit final report requesting withdrawal of the IND per FDA regulations.

7.6.3 Emergency Use of a Device

Investigator Responsibilities

In order to treat a patient with an unapproved device in an emergency situation, an investigator, who must be a licensed physician, must:

1. Confirm that the disease is serious or immediately life-threatening, that there are generally no acceptable alternatives for the treatment, and that there is not sufficient time to use existing procedures to get FDA approval for use.
2. Obtain and document informed consent from the subject or the subject's legal representative unless the circumstances meet the exception under FDA regulations at 21 CFR 50.23 which permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:
 - a. The subject is confronted by a life-threatening situation necessitating the use of the test article;
 - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
 - c. Time is not sufficient to obtain consent from the subject's legally authorized representative;
 - d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

3. Obtain the concurrence of the Chair or Vice-Chair. At Connecticut Children's, the concurrence of the Chair or Vice-Chair satisfies the requirement to obtain clearance from the Institution
4. Obtain the assessment, in writing, of a physician who is not participating in the study or in the care of the patient that concurs with the planned usage; and
5. Obtain authorization from the IDE sponsor, if an IDE exists for the device.
6. After the emergency use:
 - ☐ Report to the FDA within 5 working days of the use of the device; the report should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed.
 - o A second use of an unapproved device may not take place until approval of an IDE for the proposed use has been issued by the FDA.
 - ☐ If an unanticipated problem involving risk to subjects or others (e.g., an SAE that was unexpected and related) occurred in connection with the emergency use, submit reports consistent with the reporting requirements of the IRB, the FDA, and the manufacturer of the test article.

IRB Responsibilities

The HRPP Medical Director/IRB Chair and/or Vice Chair will:

1. Provide advice and assistance regarding interpretation of FDA regulations.
2. Review reports of emergency use, review exemptions from the requirement to obtain consent, and determine if the use met the FDA regulatory requirements.
3. If requirements not met, inform provider about appropriate process for future use.
4. If requirements were met, provide a letter from the IRB acknowledging the emergency use.

7.7 Expanded Access of Investigational Drugs & Devices

Expanded access is a regulatory pathway for treatment of a patient with a serious or life-threatening disease or condition using an investigational drug, biologic, or device. It is intended for patients who:

- Have serious or immediately life-threatening diseases:
 - Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day

functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. ([21 CFR 312.300](#))

- Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. ([21 CFR 312.300](#))
- Have no comparable alternatives
- Cannot enroll in a clinical trial

Expanded access is intended to diagnose, monitor, or treat a patient's condition rather than obtain info about the safety or effectiveness of the investigational drug or device. Expanded access can also be referred to as "compassionate use."

The term "compassionate use" does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.

7.7.1 Expanded Access of Investigational Drugs

There are three categories of expanded access of investigational drugs:

- Expanded access for individual patients, including for emergency use (as outlined above)
- Expanded access for intermediate-size populations which will be referred for review by the convened IRB
- Expanded access for widespread treatment use through a treatment IND/protocol which will be referred for review by the convened IRB

The following sections pertain to the processes required for expanded access for individual patients.

1. A licensed physician must determine that the patient they intend to treat has a serious or life-threatening condition and has no other comparable or satisfactory therapeutic options and the patient cannot obtain the drug under another IND or protocol
2. The licensed physician can request a waiver of the requirement for full IRB review from the FDA using Form 3926 (by selecting the appropriate box on the

form to request a waiver) or by submitting a separate waiver request with the FDA 1571 application

- When a waiver is requested, the IRB Chair concurrence process can be utilized as long as the FDA has granted a waiver under 56.105 of the requirements in 56.108.
- If a waiver is not requested, the individual expanded access will be referred for review and approval by the convened IRB before treatment use begins.

IRB Submission Requirements

The following is required when requesting an expanded access for an individual patient:

- o Submit expanded access application before treatment use begins via electronic submission system which includes:
 - o A thorough patient history and treatment plan (which can be included in the Form FDA 3926 or in another document)
 - o The proposed daily dose, route, and frequency of administration, duration of planned duration of planned treatment, criteria for discontinuation of treatment, and planned dose modifications for adverse events; The planned monitoring for adverse events, response to treatment, and changes in clinical status, as well as proposed modifications to the treatment plan to mitigate risks to patients if appropriate;
 - o The key details of the patient's history, including diagnosis and summary of prior therapy (including response to such therapy), the reason for request, including an explanation of why the patient lacks other therapeutic options; and information regarding a patient's relevant clinical characteristics (such as comorbid conditions and concomitant medications) that is necessary to assess the potential for increased risks of the drug;
 - o A summary of known risks of the drug
 - o An assessment that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition.
 - o A consent form that contains the information required under 21 CFR 50.25
 - o The Investigator's Brochure (if available)
 - o The FDA-issued individual patient expanded access IND.

IRB Review

IRB review will proceed via the Chair concurrence pathway described in 7.6.3.3 unless the Chair/Vice-Chair determines that convened IRB review is needed (in which case the processes required for convened IRB review will be followed).

Post-Approval

The investigator is responsible for complying with FDA and other regulatory requirements and policies, including, but not limited to, obtaining prospective IRB approval of proposed modification to the treatment plan, prompt reporting of

unanticipated problems, non-compliance, submitting continuing reviews and study closure, as applicable.

7.7.2 Expanded Access of Investigational Devices

There are three categories of expanded access of investigational devices:

- Emergency use, as outlined above
- Expanded access for single patient or small group (also referred to as compassionate use)
- Expanded access for widespread treatment use through a treatment IDE/protocol which will be referred for review by the convened IRB

The following sections pertain to the processes required for expanded access of investigational devices for individual patients/small groups:

1. A licensed physician must determine that the patient they intend to treat has a serious or life-threatening condition, that there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition exists, the potential patient benefit justifies the potential risks of the investigational device.
2. The licensed physician must request IRB Chair concurrence before proceeding with the treatment use.

IRB Submission Requirements

The following is required when requesting an expanded access of an investigational device for an individual patient/small group:

- o Submit expanded access application before treatment use begins via electronic submission system which includes:
 - o A thorough patient history and treatment plan
 - o Rationale for proposed treatment
 - o An assessment that the probable risk to the patient from the investigational device is not greater than the probable risk from the disease or condition.
 - o A plan for monitoring
 - o An independent assessment of a physician who is not participating in the study or in the care of the patient that concurs with the planned usage;
 - o A consent form that contains the information required under 21 CFR 50.25
 - o Authorization from the device manufacturer on the use of the device.
 - o Documentation of FDA approval for the expanded access of the investigational device
 - o If there is an IDE for the device, confirmation of the IDE by the sponsor
 - o If there is no IDE for the device: A description of the device provided by the manufacturer

IRB Review

IRB review will proceed via the Chair concurrence pathway described in 7.6.4.3 unless the Chair/Vice-Chair determines that convened IRB review is needed (in which case the processes required for convened IRB review will be followed).

Post-Approval

The treating physician (or whoever submitted the original expanded access request) must submit a follow-up report to the FDA within 45 days of using the investigational device. If any problems occurred as a result of device use, these must also be reported to the FDA and reviewing IRB as soon as possible. The investigator is responsible for complying with FDA and other regulatory requirements and policies, including, but not limited to, obtaining prospective IRB approval of proposed modification to the treatment plan (unless necessary to eliminate apparent immediate hazard to the participant), prompt reporting of unanticipated problem, non-compliance, submitting continuing reviews, and study closure, as applicable. The review may be conducted by the Chair or a designee.

7.7.3 IRB Review of Individual Expanded Access of Drugs & Devices

- The IRB will review to ensure all necessary materials have been included as described above.
- The reviewer will disclose any conflicting interest; if there is a conflict of interest, the submission will be re-assigned.
- The reviewer will:
 - o Assess the risks and benefits of treatment for the particular patient involved, whether risks to the patient have been minimized and that such risks are reasonable in relation to anticipated benefits
 - o When the request is for a pediatric patient, confirm that adequate provisions are included for soliciting age-appropriate assent from children and permission from a parent or guardian, as required under 21 CFR 50.55;
 - o Confirm that the informed consent document contains the information required under 21 CFR 50.25;
 - Given that the drug/device used under expanded access is investigational, a statement in the informed consent document indicating that although the primary use of the drug/device is for treatment, the drug/device is investigational and FDA has not determined that the drug/device is safe or effective for use in treating the condition, will satisfy the requirement under 21 CFR §50.25(a)(1) that the informed consent provide a statement that the use of the product “involves research.”
 - o Confirm the validity of the IND or IDE (if applicable) number
 - o The reviewer documents their review and determinations via the expanded access checklist.
 - o The reviewer establishes the continuing review frequency.

- o The Chair or Vice Chair CPHS will provide a statement of concurrence to the investigator via the electronic submission system.
- o Continuing review and the review of amendments and reportable events may also occur via the concurrence pathway.
- o At any time, the reviewer may forward the submission to the full board.

7.8 Planned Emergency Research

In the event that a study is proposed that involves planned emergency research, the HRPP will utilize the applicable Appendix of this document to guide the review process.

7.9 Humanitarian Use Devices (HUD)

In accordance with 21 CFR 814.124, treatment with a HUD is subject to full board initial and continuing review by the IRB. At the time of review, the IRB will determine if written consent from participants for use of the HUD is necessary. If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, the investigator is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use. It is the responsibility of the investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval. Investigators are reminded that Humanitarian Device Exemptions are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application.

8 Reportable New Information

8.1 Policy

Connecticut Children's complies with DHHS and FDA regulations which state that institutions must have written policies on reporting the following to the IRB, institutional officials, and relevant federal agencies and departments: unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the policies contained here or the requirements or determinations of the IRB.

The following procedures describe how these reportable events are managed in research under the auspices of Connecticut Children's.

8.2 Definitions

Unanticipated problem involving risks to subjects or others: Any information, including any incident, experience, or outcome that meets **ALL** of the following conditions:

1. **Unexpected** (in terms of nature, severity, or frequency) given the procedures described in the protocol-related documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied;
2. **Related or possibly related** to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. **Harmful**: suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Non-compliance. Non-compliance is defined as a failure to comply with any of the regulations and policies described in this document, or failure to follow the requirements and determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious non-compliance: noncompliance that may affect participant safety, increase risks to participants, decrease potential benefits, violate the rights and welfare of participants, compromise the integrity of the study data, or affect participant's willingness to participate in research.

Continuing non-compliance: a pattern of non-compliance that suggests a likelihood that instances of non-compliance will continue without intervention. The pattern of noncompliance is assessed by:

- the number of incidents occurring during the course of a protocol, or across multiple protocols,
- whether the same noncompliant action was repeated or many different noncompliant events occurred especially after education or training has been provided to the researcher or research staff

Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

Allegation of Non-Compliance: an unproved assertion of non-compliance.

Finding of Non-Compliance: an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator that the protocol was willfully not followed would represent reports of non-compliance that would require no

further action to determine their truth and would therefore represent findings of non-compliance.)

8.3 Procedures

8.3.1 Reporting to the IRB

The following examples under each category must be reported to the IRB:

- **New or Increase in Risk:** Information that indicates a new or increased risk, or a safety issue. For example:
 - New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk or uncovers a new risk.
 - An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or to describe a new risk.
 - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
 - Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.
 - Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.
- **Harm/Death:** Any harm (including death) experienced by a subject or other individual(s) that, in the opinion of the investigator, is unexpected and at least probably related to the research procedures
 - A harm is “unexpected” when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
 - A harm is “probably related” to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.
- **Non-compliance:** Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB that causes harm, increases the risk of harm, adversely affects the rights or welfare of participants or undermines the scientific integrity of the data, or an allegation of such non-compliance.
- **Audit:** Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483)

- **Reports:** Written reports of study monitors, internal audit reports, data safety monitoring reports, etc. that impact the safety of participants or influence the conduct of the study.
- **Protocol deviation:** An accidental or unintentional change to the IRB approved protocol that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- **Confidentiality:** Breach of confidentiality.
- **Planned protocol deviation:** In non-urgent/emergent situations, a request for IRB approval of a single subject or “one time” protocol amendment; approval from the study sponsor or medical monitor may also be necessary but by itself is not sufficient. If the investigator anticipates that there will be future requests for the same deviation, then the protocol should be amended.
- **Unreviewed Change:** Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- **Incarceration:** Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- **Complaint:** Complaint of a subject that cannot be resolved by the research team.
- **Suspension:** Premature suspension or termination of the research by the sponsor or investigator.
- **Unanticipated Adverse Device Effect:** Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- **Non-serious and non-continuing non-compliance:** In scenarios where the IRB has instructed the research team to submit an RNI, the research team may choose this option if they do not think any of the other categories apply and the circumstances resulted in non-compliance that is non-serious and non-continuing.
- **Pregnancy of Participant receiving an intervention:** Scenarios where a participant receiving an intervention becomes pregnant. Please note that if the research team will be collecting data on the pregnancy and/or outcome, a separate amendment is needed if the application does not describe this data collection.
- **Revised investigator brochure or supplemental guidance for Investigators:** No new risks or increased frequency/magnitude of previously known risks.

8.3.2 Timelines for Reporting to the IRB

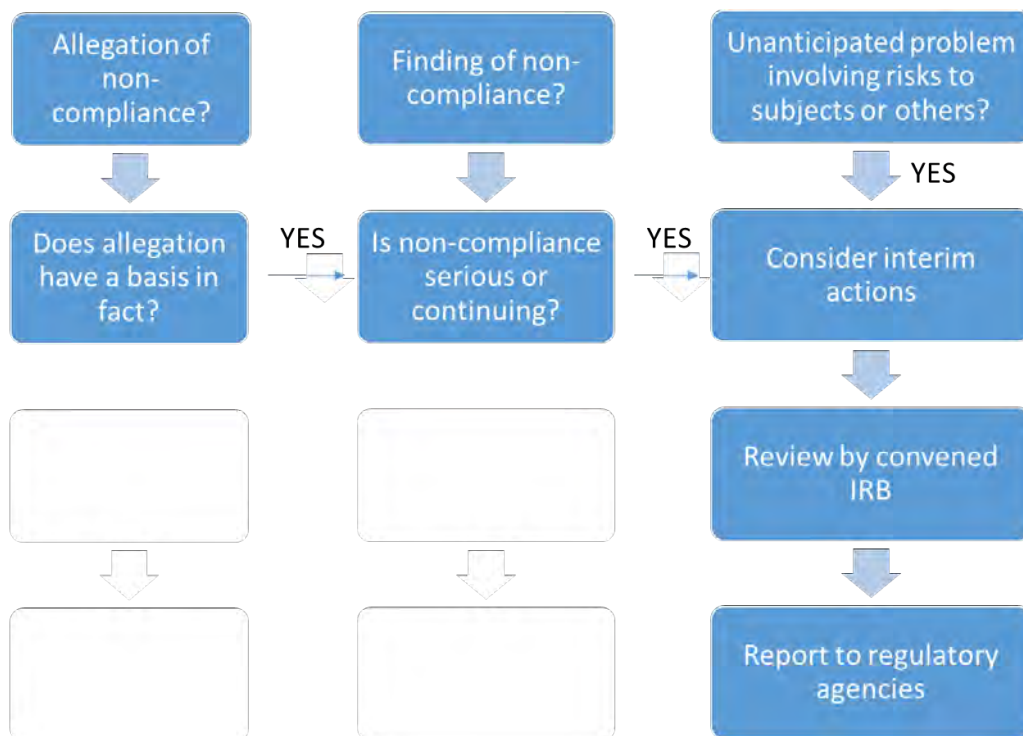
Death of a Connecticut Children's participant that is unanticipated and related: within 5 calendar days of knowledge or notification

Events that meet one or more of the categories listed in 8.3.1: within 5 business days of knowledge or notification

Events that do not meet at least one of the categories listed in 8.3.1: should be summarized at the time of next continuing review

8.3.3 IRB Review Process

1. IRB staff will review the reportable new information for completeness and request any additional information that is necessary.
2. IRB Chair/HRPP Medical Director/HRPP Director will evaluate the report along with all pertinent study materials such as the last IRB approval letter, IRB application, protocol, consent documents, and any other relevant documents utilizing the below flowchart



- a. If any question results in a “No” answer, the event will be managed administratively and an acknowledgement letter will be sent to the PI, contact, and party who reported the event, if applicable.
- b. If the IRB Chair/HRPP Medical Director/HRPP Director cannot determine the categorization of the event, the event

may be sent to the full IRB for review or an inquiry may be initiated, as follows:

The IRB Chair or his/her designee appoints the members of the inquiry committee based on the expertise and background needed to answer the question and charges the committee with the question to be answered which may include: review of the protocol, review of the sponsor or other audit report of the investigator, if appropriate; review of any relevant documentation, including consent documents, case report forms, subject's investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human subjects; and interview of appropriate personnel if necessary;

The inquiry committee carries out these procedures within 60 days.

The inquiry committee may seek counsel of other institutional offices/entities as appropriate.

The inquiry committee provides a written or oral report of the committee's decision to the IRB Chair or his/her designee which is then presented to the full IRB.

4. Based on the information received from the investigator, the IRB Chair or designee, HRPP Medical Director, or HRPP Director may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee, the HRPP Medical Director, or HRPP Director must be reported to a meeting of the convened IRB.
5. The primary reviewer will be given the event report, protocol, consent form, and recommendations from the IRB Chair or designee, when appropriate. All IRB members will receive the event report. After review of the protocol and event report, the full IRB will determine if additional information is necessary or classify the event as:
 - a. an allegation of non-compliance with no basis in fact
 - b. non-compliance that is neither serious nor continuing non-compliance
 - c. serious or continuing non-compliance
 - d. an unanticipated problem involving risks to subjects or others
 - e. none of the above
6. The IRB can make the following recommendations:
 - a. Modify the protocol
 - b. Modify the information disclosed during the consent process
 - c. Provide additional information to current subjects, whenever the information may relate to the subject's willingness to continue
 - d. Provide additional information to past subjects
 - e. Ask current subjects re-consent
 - f. Increase the frequency of continuing review
 - g. Observe the research
 - h. Observe the consent process
 - i. Require additional training of the investigator
 - j. Notify investigators at other sites
 - k. Terminate IRB approval (see section 3.10.1)
 - l. Suspend IRB approval (see section 3.10.1)

- m. Transfer subjects to another investigator
 - n. Make arrangements for clinical care outside the research
 - o. Allow continuation of some research activities under the supervision of an independent monitor
 - p. Require follow-up of subjects for safety reasons
 - q. Require adverse events or outcomes to be reported to the IRB and the sponsor
 - r. Obtain additional information
7. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others, serious non-compliance, or continuing non-compliance, the IRB will:
- a. Notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, and the investigator's Division Chief or supervisor, and
 - b. Report its findings and recommendations to the Institutional Official and others as outlined in Section 10 (including federal officials as appropriate).

8.3.4 Reconsideration of the IRB Decision

The notice to the investigator of the IRB determination will inform the investigator that he or she has ten (10) business days from receipt of the notice to request reconsideration of the IRB decision by sending the IRB a written request for reconsideration including the basis of the investigator's request.

- a. If an investigator requests reconsideration, the investigator's written request is considered at the next IRB meeting (by the initial reviewing committee) and the IRB makes a determination whether to uphold, reverse or modify its decision. The IRB notifies the investigator of the final outcome.
- b. If the IRB receives a request for reconsideration from the investigator, the IRB should notify the Institutional Official of the request and of the final outcome.

9 Complaints and Non-compliance

9.1 Policy

As part of its commitment to protecting and promoting the rights and welfare of human subjects in research, Connecticut Children's reviews all complaints and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research. When making determinations regarding non-compliance, the IRB will assess

each allegation in context on a case-by-case basis.

The following procedures describe how complaints and allegations of non-compliance are handled by the IRB.

9.2 Complaints

The IRB Chair, HRPP Medical Director, or HRPP Director will promptly handle (or delegate staff to handle) and, if necessary, investigate all complaints, concerns, and appeals received by the IRB/HRPP Office. This includes complaints, concerns, and appeals from investigators, research participants and others, as well as possible non-compliance identified in conjunction with the Research Compliance Manager.

Complaints can be received by email, telephone, compliance hot-line, or in-person. Upon receipt of the complaint, the HRPP team member will provide all of the information pertinent to the complaint to the HRPP Medical Director and HRPP Director who will make a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 3.10.1 will be followed.

If the complaint meets the definition of non-compliance or an unanticipated problem involving risks to subjects or others, it will be handled according to section 8.

9.3 Non-compliance

Investigators and their study staff are required to report instances of possible non-compliance, according to the Reportable New Information in Section 8. The Principal Investigator is responsible for reporting any possible non-compliance by study personnel to the IRB Office. However, any individual or employee may report observed or apparent instances of non-compliance to the IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any IRB and/or institutional review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the IRB Chair, HRPP Medical Director, or HRPP Director directly to discuss the situation informally.

The Research Compliance Manager will report to the HRPP Medical Director or Director any possible non-compliance that may involve risks to subjects within 24 hours.

10 Reporting to Regulatory Agencies and Institutional Officials

10.1 Policy

Federal regulations require prompt reporting to appropriate institutional officials, and (for certain federally funded research) the department or agency head of: (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. The IRB/HRPP Office will comply with this requirement and the following procedures describe how these reports are handled.

10.2 Procedures

1. IRB/HRPP staff will initiate these procedures as soon as the IRB takes any of the following actions:

- a. Determines that an event is considered an unanticipated problem involving risks to participants or others;
- b. Determines that non-compliance was serious or continuing;
- c. Suspends or terminates approval of research.

2. The HRPP Director or designee is responsible for preparing reports or letters which includes the following information:

- a. The nature of the event (e.g., unanticipated problem involving risks to participants or others; serious or continuing non-compliance; suspension or termination of approval of research);
- b. Name of the institution conducting the research;
- c. Title of the research project and/or grant proposal in which the problem occurred;
- d. Name of the principal investigator on the protocol;
- e. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- f. A detailed description of the problem, including the findings of the organization and the reasons for the IRB's decision;
- g. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.);
- h. Plans, if any, to send a follow-up or final report by the earlier of:
 1. A specific date;
 2. When an investigation has been completed or a corrective action plan has been implemented.

4. The IRB Chair, Medical Director, and the IO review the letter and modify the letter/report as needed.
 5. The HRPP Director and/or HRPP Medical Director sign the report.
 6. The HRPP Director or designee sends a copy of the report to:
 - a. The Principal Investigator
 - b. The IRB by including the letter in the next agenda as an information item
 - c. The Institutional Official;
 - d. The following federal agencies (note: the Institutional Official is the signatory for reporting to federal agencies):
 - OHRP, if the study is subject to DHHS regulations or subject to a DHHS federalwide assurance
 - FDA, if the study is subject to FDA regulations.
 - DoD, if the study is subject to DoD regulations
 - If the study is conducted or funded by any Federal Agency other than DHHS and DOD that is subject to “The Common Rule”, the report is sent to OHRP or the head of the agency as required by the agency.
- Note: Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.

7. In cases where the convened IRB has determined that an occurrence constitutes serious or continuing non-compliance, or constitutes an unanticipated problem involving risks to subjects or others, and the IRB has suspended or terminated the research, the following will also be notified as appropriate to the context:

- i. Sponsor, if the study is sponsored (note: the IO, HRPP Director, or HRPP Medical Director is signatory for notifications to sponsors);
- ii. Contract research organization, if the study is overseen by a contract research organization;
- iii. Department Head or other supervisor of the principal investigator;
- iv. The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from that covered entity;
- v. The Information Security Officer of an organization if the event involved violations of information security requirements of that organization;
- vi. Legal Department;
- vii. Risk Manager
- viii. Compliance Department;
- ix. Other Connecticut Children’s Departments or officials that require notice, as determined by the HRPP Director (e.g.,

Pharmacy, Research, Grants and Sponsored Programs, etc.);

- x. Others as deemed appropriate by the Institutional Official.

The HRPP Director ensures that all steps of this policy are completed promptly (within 30 days of final review by the IRB). A copy of the final report is maintained in the IRB/HRPP office.

11 Investigator Responsibilities

11.1 Policy

Principal Investigators (PIs) are ultimately responsible for the conduct of research. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

The following procedures describe the investigator responsibilities in the conduct of research involving human participants.

11.2 Investigators

Principal Investigators

The IRB recognizes one Principal Investigator (PI) for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the PI must be modified to meet the investigator's skills or have one or more additional qualified faculty as Co-investigator(s).

Student Investigators

Students may serve as a PI if they otherwise fulfill all eligibility criteria for the study, and have a faculty sponsor who serves as a co-investigator and supervises the conduct of the research. Only faculty or staff members may serve as a faculty sponsor on a research project involving human subjects. Adjunct faculty of Connecticut Children's and/or any investigator whose status is considered to be "in training" (i.e. students and medical residents) may not serve as a faculty sponsor but may serve as a co-investigator.

Research Team

The PI and other individuals, also known as key personnel (involved in the design, conduct, or reporting of the human research activities), who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol.

11.3 Responsibilities

In order to satisfy the requirements of this policy, investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. Have sufficient resources necessary to protect human subjects, including:
 - a. Access to a population that would allow recruitment of the required number of subjects;
 - b. Sufficient time to conduct and complete the research;
 - c. Adequate numbers of qualified staff;
 - d. Adequate facilities;
 - e. A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions;
 - f. Availability of medical or psychological resources that subjects might require as a consequence of the research.
4. Maintain appropriate oversight of each research study, including the recruitment, consent and protocol procedures, and retain ultimate responsibility for the conduct of those whom they delegate responsibility, including research staff and trainees.
5. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Connecticut and the policies of Connecticut Children's;
6. Assure that all key personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
7. Assure availability to research staff when needed.
8. Protect the rights and welfare of prospective subjects;
9. Ensure that risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
10. Recruit subjects in a fair and equitable manner;
11. Obtain and document informed consent as required by the IRB and ensure that no human subject is involved in the research prior to obtaining their consent;

12. Have plans to monitor the data collected for the safety of research subjects (where appropriate);
13. Protect the privacy of subjects and maintain the confidentiality of data;
14. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with intellectual disabilities, or economically or educationally disadvantaged persons, include additional safeguards in the study to protect the rights and welfare of these subjects;
15. Have a procedure to receive complaints or requests for additional information from subjects and respond appropriately;
16. Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and research staff;
17. Ensure that all research involving human subjects receives IRB review and approval in writing before commencement of the research;
18. Comply with all IRB decisions, conditions, and requirements;
19. Ensure that protocols are submitted in a way that allows for timely continuing IRB review and approval;
20. Report unexpected or serious adverse events problems that require prompt reporting to the IRB (see Section 8)
21. Obtain IRB review and approval in writing before changes are made to approved protocols or consent forms;
22. Seek IRB assistance when in doubt about whether proposed research requires IRB review.
23. For DOD-funded research, submit surveys to be performed on DOD personnel for review and approval by the DOD after the research protocol is reviewed and approved by the IRB.

11.4 Training / Ongoing Education of Investigators and Research Team

As stated above, one component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. Connecticut Children's is committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

11.4.1 Orientation

All Principal Investigators and members of their research team (also known as "key personnel") must review core training documentation including the "Connecticut

Children's Standard Operating Policies and Procedures for Human Research Protection," and the "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." In addition, the Research Compliance Manager typically meets with new principal investigators of clinical trials, and principal investigators of investigator-initiated clinical studies, to review responsibilities and offer assistance with research monitoring and education of staff. Any investigator may require this service, or the IRB may request that such consultation take place. Lastly, Principal Investigators and research team members may request individualized training on a variety of topics, including:

- **IRB 101** training is recommended for all new research staff. This training provides a brief overview of the Connecticut Children's Human Research Protection Program and the IRB review process.
- **IRBManager Orientation** refers to a general overview of the IRBManager system. This training is most useful for new research staff who want to know the general functions and navigation of IRBManager.
- **IRBManager Advanced** training refers to a higher level of IRBManager training designed for personnel who are in charge of managing multiple study submissions in IRBManager. In addition to the general orientation, IRB staff will go into more details about submission-specific requirements, responding to revisions requested, and other important functionality within the IRBManager system.
- **Research Compliance Training** is coordinated with the Assistant Manager Clinical Research Compliance and may include topics such as consenting, biospecimen transport and tracking, navigating regulatory requirements and documentation best practices. These trainings can be an individual or a small group and tailored to your study/research experience.
- **Reliance/Single IRB training** is recommended for anyone wishing to rely on an external IRB for a multisite research study. This training provides a brief overview and key considerations of external sIRB reliance, including awareness of study personnel roles and responsibilities to the sIRB (reviewing IRB) as well as our local Connecticut Children's IRB (relying IRB).
- **Other training** may refer to any other HRPP related training which the IRB will help to provide or coordinate for you.

11.4.2 Initial Education

The PI and key investigators must complete the Connecticut Children's Required Core Modules in the CITI Course in the Protection of Human Research Subjects.

New research protocols will not be accepted from principal investigators who have not

completed the initial education requirement.

For all research, training of study personnel must be current at the time of initial approval. Training must also be current for an individual added to a study through a request for modification. Training will be considered current if completed within the past three years.

Acceptance of Alternative Initial and Continuing Education

If investigators or members of their research team can verify that they have successfully completed human subjects research training equivalent to that required by the Connecticut Children's HRPP (as determined by the HRPP Director and HRPP Medical Director), they may request acceptance of an alternative requirement for Initial and continuing Education. For example, the IRB may use its discretion to accept comparable non-expired CITI training that was completed under another Institution or other appropriate training platforms.

11.4.3 Continuing Education and Recertification

All investigators and members of their research teams must meet HRPP continuing education requirements every three (3) years after certification of Initial Education for as long as they are involved in human subject research. Training includes review of the appropriate refresher modules (specified by the HRPP Office) at the CITI web-based training site. As noted above, the IRB may use its discretion to accept comparable non-expired CITI training refresher modules.

Investigators who are also IRB Chair, IRB members, or IRB/HRPP Office staff will satisfy the training requirements for IRB members and staff described in this policy under Section 2.13.

11.4.4 Additional Resources

Human research protection information will be made available on the IRB/HRPP internal and external websites on an ongoing basis to ensure that the Connecticut Children's research community is apprised of current regulatory and policy requirements and training opportunities.

11.5 Investigator Concerns

Investigators who have concerns or suggestions regarding the Connecticut Children's human research protection program should convey them to the Institutional Official or other responsible parties (e.g., departmental Chair) regarding the issue, when appropriate. The Institutional Official will research the issue, and

when deemed necessary, convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the IRB Chair, HRPP Medical Director, and HRPP Director will be available to address investigators' questions, concerns and suggestions.

12 Sponsored Research

12.1 Policy

It is Connecticut Children's policy that any sponsored research conducted under the auspices of Connecticut Children's is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

12.2 Definitions

Sponsor. Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

Sponsored research. Sponsored research means research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices or biologics.

12.3 Responsibility

- 1) Sponsor contracts are reviewed by General Counsel personnel. The legal team will review contracts and the IRB and Office for Sponsored Programs (OSP) will share contract and study information as necessary for each sponsored protocol to ensure that protocol, consent, and contract language are consistent.
- 2) Contracts will be reviewed for the following by the legal team:
 - a) Sponsor contracts will indicate that Connecticut Children's will follow the protocol, applicable regulations and its ethical standards.

The following additional requirements apply to Sponsor contracts for which there is room for negotiation.

- b) When appropriate, the contract and consent form specify that medical care for research related injuries is available (e.g. Contracts for investigational drug studies shall specify that medical care for research related injuries is available.) When appropriate, the contract and consent form also address

who pays for medical care for research related injuries. The research-related injury information in the contract must be consistent with the research-related injury information in the consent form. If the contract does not involve an investigational drug, the legal team will consult with the HRPP Director or the HRPP Medical Director to determine if information regarding research-related injury is required in the contract and consent form based on whether medical care for research-related injury might be needed.

- c) If the sponsor will monitor the conduct of the research, the contract will be required to state that the sponsor will send data and safety monitoring plans and reports to Connecticut Children's in accordance with the data and safety plan approved by the IRB of record for Connecticut Children's.
- d) If the study monitor/sponsor uncovers information that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study, the sponsor will make sure that the information is communicated to Connecticut Children's IRB promptly (no longer than 30 days).
- d) If the sponsor discovers results that could affect participants' safety or medical care, the sponsor will make sure the IRB is notified.
- e) The sponsor contracts will specify the steps followed to communicate findings from a closed research study to the investigator or Connecticut Children's when those findings directly affect participant safety. The sponsor contract will also specify a time frame after closure of the study during which the sponsor will communicate such findings.
- f) The sponsor contracts will specify the plans for disseminating the findings from the research and the roles that the sponsor and Connecticut Children's will play in the publication or disclosure of results.

13 Conflict of Interest in Research

13.1 Policy

The policy of Connecticut Children's is to comply with the Public Health Services' (PHS) policy 42 CFR Part 50 and 45 CFR Part 94, "Responsibility of Applicants for promoting Objectivity in Research for which Public Health Service Funding is Sought and Responsible Prospective Contributors" (August 2011). These requirements apply to all research conducted at Connecticut Children's (PHS-funded and non-PHS funded) unless otherwise noted in this policy.

All investigators engaged in research at Connecticut Children's are responsible for disclosing potential conflicts of interest that may influence the design, conduct, results and/or reporting of research, or may compromise or have the appearance of compromising the integrity of the research at the institution.

In addition, the Finance and the Foundation notify the IRB about any potential institutional conflicts of interest which are then evaluated by the Corporate Compliance Conflict of Interest Committee in accordance with the institutional conflict of interest policy.

13.2 Definitions

1. Conflict of Interest – Any financial or non-financial arrangement, situation, or action that affects or is perceived to affect the design, conduct, or reporting of research.
2. Disclosure: An investigator or other key research personnel's disclosure of significant financial interests or nonfinancial interests to Connecticut Children's.
3. Entity –**Any** domestic or foreign, public or private, organization (excluding a Federal agency) from which an Investigator (and spouse and dependent children) receives remuneration or in which any person has an ownership or equity interest.
4. Financial Conflict of Interest (FCOI)- A Financial Conflict of Interest exists when the Institution, through its designated official(s), reasonably determines that an Investigator's Significant Financial Interest is related to a research project and could directly and significantly affect the design, conduct or reporting of the research.
5. Immediate Family: Spouse or domestic partner and dependent children.
6. Institutional Responsibilities – An investigator's professional responsibilities on behalf of Connecticut Children's which may include for example: research activities, research consultation, teaching, professional practice, institutional committee memberships and service on panels such as the Institutional Review Board or Data and Safety Monitoring Boards.
7. Investigator – All personnel responsible for the design, conduct or reporting of research. This includes individuals who recruit and obtain consent from participants and/or analyze data.
8. Significant Financial Interest ("SFI"): A financial interest consisting of one or more of the following interests of the Investigator (and those of the Investigator's spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities:
 - a. Compensation from any entity exceeding \$5,000
 - b. With regard to any publicly traded entity, when the value of any remuneration (includes salary and any payment for service not otherwise identified as salary, for example, consulting fees, honoraria, paid authorship, teaching engagements, service on advisory committees) received from the entity in the twelve months preceding the disclosure aggregated with the value of any equity interest (includes any stock, stock option, or other ownership interest as

determined through reference of public prices or with other reasonable measure of fair market value) in the entity as of the date of disclosure exceeds \$5,000.

- c. With regard to any non-publicly traded entity, when the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated, exceeds \$5,000, or any equity in the entity
 - d. Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests.
 - e. Board position or executive level relationship related to the entity, regardless of compensation
 - f. Travel that is reimbursed (i.e., Investigator is made whole for the financial outlay required) or sponsored (i.e., the costs are paid on behalf of the Investigator such that the exact monetary value may not be readily available)
 - i. Applicable only to PHS-funded investigators
 - ii. The \$5000 de minimis means an Investigator only has to report travel if a reasonable estimate for that travel exceeds \$5000, the investigator earns more than \$5000 from the entity sponsoring or reimbursing the travel, or the combination of the two exceed \$5000.
 - iii. Excludes travel reimbursed/sponsored by CCMC, a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education.
 - g. *Exclusions:* Does not include the following types of financial interests: salary, royalties, or other remuneration paid by the Institution to the Investigator if the Investigator is currently employed or otherwise appointed by Institution, including intellectual property rights assigned to the Institution and agreements to share in royalties related to such rights; any ownership interests in the Institution held by the Investigator, if the Institution is a commercial or for-profit organization; income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles; income from seminars, lectures, or teaching engagements or reimbursed/sponsored travel when sponsored by a Federal, state, or local government agency, an institution or higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education; or income from service on advisory committees or review panels for a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education.
9. Public Health Service (PHS) - Public Health Service of the United States Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated, including but not limited to

National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ), Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration, Centers for Medicare and Medicaid Services (CMS), Indian Health Service, Substance Abuse and Mental Health Services Administration (SAMHSA)

10. PHS Funded Research – Research that includes funding by means of a PHS grant, PHS contract, or PHS cooperative agreement.
11. Research - A systematic investigation designed to develop or contribute to generalize knowledge relating broadly to public health, including behavioral and social sciences research. The term encompasses basic and applied research, and product development.

13.3 Individual Conflicts of Interest

13.3.1 Investigator Responsibilities:

All investigators must complete an Annual Disclosure of Significant Interests form. In addition, the IRB application, which is required for initial review of research involving human subjects, prompts all investigators involved to complete an annual disclosure form, if not already done, or amend the annual disclosure form if changes are necessary based on their engagement in the proposed research study.

1. Disclose any significant financial interests (SFIs) related to their institutional responsibilities including any SFIs of immediate family members
 - a) PHS-funded Investigators disclose the following in regard to Travel:
 - (1) The purpose of the trip;
 - (2) The identity of the sponsor/organizer of the trip;
 - (3) The destination of the trip; and
 - (4) The duration of the trip.
2. Submit disclosures:
 - a) At the time of application for initial approval of research
 - b) At the time of a modification to add an individual to an existing research study.
 - c) Annually
 - d) Updated within 30 days of discovering or acquiring a new SFI
 - e) No later than at the time of application for PHS-funded research
3. Provide in a timely manner any information related to their disclosed interests that Connecticut Children's, in its discretion, deems relevant to its review and FCOI assessment.
4. Cooperate fully with the Research Conflict of Interest Committee, if applicable;
5. Comply with COI management plans, if applicable;
6. Comply with COI training requirements.

13.3.2 Institutional Review Procedures for Disclosures:

1. Disclosure submission and review process

- i. Disclosures for research not involving human subjects:
 - 1. Submitted to the Office for Sponsored Programs (OSP)
 - 2. Representative(s) from OSP will forward any disclosures that appear to involve SFIs to the Research Conflict of Interest Committee (RCOIC) for review.
 - 3. The RCOIC will forward their recommendations to the OSP who will provide the outcome of the disclosure review to the relevant parties as outlined in the Notifications section.
- ii. Disclosures for research involving human subjects:
 - 1. Submitted to the Human Research Protection Program (HRPP)
 - 2. Representative(s) from the HRPP will forward any disclosures that appear to involve SFIs to the RCOIC for review.
 - 3. The RCOIC will forward their recommendations to the IRB for a final decision regarding management. The IRB retains the final authority to decide whether the conflicting interest and its management, if any, allows the research to be approved, and to make final determinations that participants are protected.
 - 4. The IRB will notify the relevant parties, as outlined in the Notifications section, regarding the outcome of the disclosure review
- iii. Notifications
 - 1. If the findings indicate that an individual's disclosure does not constitute a conflict, written notification of that decision and rationale shall be provided to the individual and the Chair or Director of the individual's department.
 - 2. If the findings indicate a conflict of interest does exist, the responsible party shall notify, as applicable: the individual, the Chair or Director of the individual's department, the Corporate Compliance Committee, and other leadership if appropriate, of the existence of the conflict and the management plan.

2. Research Conflict of Interest Committee Review

a. Membership

- Medical Director of the Human Research Protection Program
- Director of the Human Research Protection Program

- Legal Department (or designee)
- b. Review deliberations may include, but are not limited to:
 - Has all relevant information concerning the involved individual's activities been acquired (i.e., has there been full disclosure)?
 - Do the individual's circumstances represent any possible violation of federal, state, or local laws and regulations?
 - What interests are created by the financial relationships involved in the situation?
 - Do individuals or institutions receive any compensation that may be affected by the study outcome?
 - Do individuals or institutions involved in research:
 - Have any proprietary interests in the product, including patents, trademarks, copyrights, or licensing agreements?
 - Have an equity interest in the research sponsor, and, if so, is the sponsor a publicly held company or non-publicly held company?
 - Receive significant payments of other sorts (e.g., grants, compensation in the form of equipment, retainers for ongoing consultation, or honoraria)?
 - Receive fees as honoraria given by another academic institution for an academic activity such as a seminar or grand rounds?
 - Receive payment per participant or incentive payments, and are those payments reasonable (or are these incentives at a level that might lead to bias)?
 - Do the individual's financial interests exceed predetermined thresholds of acceptability, where specified?
 - Will the financial interest adversely affect the protection of participants in terms of the criteria for IRB approval?
 - Will the financial interest adversely affect the integrity, design, conduct or reporting of the research, or the integrity of the data?
 - Would the financial interest adversely affect the credibility of the Human Research Protection Program?
 - If pre-clinical research, is there a reasonable anticipation of follow-up on human subjects research in the immediate future?
 - Given the financial relationships involved, is the institution an appropriate site for the research?
 - How should financial relationships that potentially create a conflict of interest be managed? What procedures would be helpful, including but not limited to those to:
 - Collect and evaluate information regarding

- financial relationships related to research?
 - Determine whether those relationships potentially cause a conflict of interest?
 - Determine whether actions are necessary to protect human subjects and ensure that those actions are taken?
- Would the rights and welfare of human subjects be better protected by any or a combination of the following:
 - Reduction of the financial interest?
 - Disclosure of the financial interest to prospective subjects?
 - Separation of responsibilities for financial decisions and research decisions?
 - Additional oversight or monitoring of the research?
 - An independent data and safety monitoring committee or similar monitoring body?
 - Modification of role(s) of particular research staff or changes in location for certain research activities, e.g. a change of the person who seeks consent, or a change of investigator? (Note: any modifications to a research plan that was previously approved by the IRB must be approved by the IRB prior to implementation).
 - Elimination of the financial interest?
- c. Determination
 - i. Relatedness: RCOIC determines if the reported SFIs are related to, or can be affected by, the research
 - ii. Financial Conflict of Interest (FCOI): RCOIC determines if the related SFIs represent a financial conflict of interest
- d. Management
 - i. If the RCOIC identifies an FCOI, resolution includes at least one of the following:
 - 1) Elimination
 - 2) Mitigation
 - 3) Management Plan: conditions or restrictions to manage an COI include, but are not limited to:
 - Public disclosure of COI (e.g. when presenting or publishing the research);
 - For research projects involving human subjects research, disclosure of COI directly to research participants;
 - Appointment of an independent monitor capable of taking measures to protect the design, conduct, and reporting of the research against bias resulting from the COI;
 - Modification of the research plan;

- Change of personnel or personnel responsibilities, or disqualification of personnel from participation in all or a portion of the research (i.e. exclusion from participation in subject selection, consent process, clinical evaluation of subjects, data collection, data analysis, etc.);
- Reduction or elimination of the financial interest (e.g., sale of an equity interest); or
- Severance of relationships that create financial conflicts.

3. Monitoring:

- a. Monitoring of conflict of interest management plans shall generally be done through certification by conflicted individuals to the OSP or IRB that he/she is adhering to their management plan. Occasionally, monitoring may be conducted through periodic audits by a member of the Compliance Department, OSP, IRB or designee.

If it is found that an Investigator does not comply with this policy or the agreed upon conflict of interest management plan, sanctions may be issued in accordance with the Conflict of Interest Committee Guidelines.

4. Reporting

- a. Determinations and management of financial conflicts are reported to the Corporate Compliance Committee
- i. Number of disclosures received and active investigations
 - ii. Management plans/corrective actions taken for any actual conflicts of interest.

5. Appeals: In situations where the Investigator disputes the decision of the IRB relating to a conflict of interest management plan, the investigator may request a meeting with the IRB Chair and/or HRPP Director and the Institutional Official to discuss the matter and present any other information the investigator believes may be relevant. Following such meeting, the IRB Chair and/or HRPP Director may recommend to the convened IRB that it consider any appropriate changes to the conflict of interest management plan previously approved by the IRB. The IRB will report any changes to the Conflict of Interest Committee.

13.3.3 Requirements specific to PHS-funded research

1. Investigator Responsibilities – see section 13.3.1 above
2. Institutional Responsibilities
 - Subrecipients: If Connecticut Children's carries out PHS-funded research through a subrecipient (e.g., subcontractors or consortium members) and is the

awardee Institution, the Office of Sponsored Programs will incorporate as part of a written agreement with the subrecipient terms that establish whether this policy or that of the subrecipient will apply to the subrecipient's Investigators as well as the time frames within which the subrecipient must provide any information necessary to ensure that Connecticut Children's is able to meet its reporting obligations to the PHS awarding agency..

- Reporting FCOIs to PHS: The Office of Sponsored Programs will report the existence of any FCOI to the PHS awarding agency initially (prior to the expenditure of any funds), annually during the award period, and within 60 days of any subsequently identified FCOI.
- Public accessibility: Prior to expenditure of any funds under a PHS-funded research project, Connecticut Children's shall ensure public accessibility about the FCOI(s) currently held, via a written response by the Corporate Compliance/COI Committee to any requestor within five business days of a request, of information concerning any significant financial interest which was disclosed, is still held by the investigator on the research project, which is determined to be related to PHS-funded research, and which is determined to be an FCOI. The information shall consist of the information required to be provided under the FCOI regulations.
- Monitoring Compliance & Mitigation
 - i. Representatives from the Compliance Department and/or the Human Research Protection Program will monitor for compliance with the policy, documenting:
 1. Failure by the Investigator to disclose a significant financial interest that is determined by Connecticut Children's to constitute a financial conflict of interest
 2. Failure by the Institution to review or manage such a FCOI, or
 3. Failure by the Investigator to comply with a FCOI management plan
 - ii. If it is determined that an SFI that was not disclosed or reviewed in a timely manner, Connecticut Children's will:

1. Within 60 days of learning about the SFI, review to determine if it is related to PHS-funded research and if an FCOI exists.
 2. If an FCOI exists: implement, on at least an interim basis, a management plan that specifies the actions that have been, and will be, taken to manage such FCOI going forward
- iii. Retrospective review: Within 120 days of determining noncompliance, Connecticut Children's will complete a retrospective review of the Investigator's activities and the PHS-funded research project(s) to determine whether any PHS-funded research, or portion thereof, conducted during the time period of the noncompliance, was biased in the design, conduct, or reporting of such research. Connecticut Children's shall document the retrospective review as described in 42 CFR Part 50 and 45 CFR Part 94 which may result in updating the FCOI report, notifying the PHS awarding agency, and/or submitting a mitigation report as required by the federal regulations.

13.3.4 Conflict of Interest Training Requirements for Investigators

1. Conflict of interest training for both human subject and non-human subject research can be accessed through the CITI training website.
2. Training is also required at least every four years and immediately when any of the following circumstances apply.
 - The FCOI policies or procedures are revised in any manner that affects the requirements of Investigators;
 - An investigator is new to Connecticut Children's;
 - Connecticut Children's finds that an investigator is not in compliance with the Connecticut Children's FCOI policy or management plan.

13.3.5 Maintenance of Records

1. For all research: the Human Research Protection Program/Institutional Review Board will maintain records of investigator disclosures and the IRB's review and

- recommendations for such disclosures for three years
2. The Research Conflict of Interest Committee will maintain records relating to the review of disclosures and sanctions by the Executive Management Team.
 3. For PHS-funded research, records relating to all Investigator disclosures of financial interests, and its review of, and response to, such disclosures (whether or not a disclosure resulted in a determination of a financial conflict of interest) and all actions taken in pursuant to this policy or any retrospective review will be maintained for three years from the date the final expenditures report is submitted to the PHS.

13.3.6 Sanctions

The Corporate Compliance/Conflict of Interest Committee shall recommend sanctions and penalties for those who knowingly and willfully disregard the conflict of interest policy, the agreed upon conflict of interest management plan or refuse to comply with their terms. The Corporate Compliance/Conflict of Interest Committee may seek advice from the Investigator(s) Division or Department Head, IRB and the Research Directors. Such recommendations shall be forwarded to the Executive Management Team for final sanctions. Sanctions may include, but are not restricted to:

1. Letter of reprimand
2. Reassignment of duties
3. Termination of grant support
4. Adjustment of research space allocation
5. Adjustment of salary
6. Suspension or dismissal

(For more information regarding the Corporate Compliance Committee and Conflicts of Interest, please see the institutional policy titled Guideline: Evaluation and Management of Conflicts of Interest)

14 Participant Outreach

14.1 Policy

Connecticut Children's is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of research involving human participants at Connecticut Children's.

The following procedures describe how Connecticut Children's fulfills that responsibility.

14.2 Responsibility

It is the responsibility of the HRPP Director to implement (or delegate staff to implement) the procedures outlined below.

14.3 Outreach Resources and Educational Materials

1. The Connecticut Children's IRB/HRPP website provides several resources including links to the Office for Human Research Protections (OHRP) to access the Belmont Report, the OHRP pamphlet regarding research participation (*Becoming a Research Volunteer: It's Your Decision*), and the federal regulations. Participants, prospective participants, and community members may access this information from the IRB/HRPP website to increase public awareness and educate potential research participants. The IRB/HRPP website also encourages subjects, families, or others with any questions or concerns regarding participation in research to contact the HRPP Director directly, and lists appropriate contact information.
2. In addition, the Connecticut Children's Research website includes a page entitled "Participant Resources", regarding participation in clinical research. This website includes a handout which provides additional information and frequently asked questions about participation in clinical research.
3. Connecticut Children's hosts several parent advisory boards including the Family Advisory Council along with boards housed within specific clinical areas such as hematology/oncology and sickle cell disease. These groups meet to provide family perspectives to improve the care and services at Connecticut Children's. The HRPP Directors have presented at parent advisory board meetings to share information about research participation and resources available.

14.4 Evaluation

Connecticut Children's periodically evaluates its outreach activities and makes changes when appropriate. These evaluations take place in an informal, ongoing manner. All IRB/HRPP staff, members and Chairs/Co-Chairs will report both positive and negative feedback about all HRPP outreach activities to the HRPP Director. He/she will then be responsible for ensuring that the input is tracked and for implementing any changes made to improve outreach activities. He/she will summarize that material annually. In order to formally evaluate its outreach activities, the HRPP Director will determine:

1. The specific community outreach activities being used
2. Whether or not these community outreach activities have an evaluative component, and if so what, if any, changes in the outreach activities have resulted from these evaluations

The HRPP Director will annually assess the adequacy of outreach activities. This assessment will include:

1. The scope, the content and the adequacy of outreach activities and resources.
2. Whether the research community is using the website resources described above;
3. Whether the research community is using other educational materials to inform prospective participants about their rights and welfare as research participants.
4. Whether additional resources are needed to improve participant outreach activities

The results of the assessment will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.

15 Health Insurance Portability and Accountability Act (HIPAA)

15.1 Policy

Protected Health Information obtained by Connecticut Children's may not be used internally or disclosed to any outside person or organization for research purposes without prior approval of the IRB. Connecticut Children's researchers must also abide by all corporate HIPAA policies regarding HIPAA privacy and security.

The following describe the procedures for conducting research at Connecticut Children's in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

15.2 Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Authorization. An authorization is a detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

Covered entity. Covered entity is the term applied to institutions that must comply with the Privacy Rule. These include:

- Health plans
- Health care clearinghouses
- Health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.

Common Rule. Common Rule is a federal Policy on human subject protection that provides for the primary source of regulation of research.

De-Identified Information. De-Identified Information is health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual. If information is de-identified, it no longer is subject to the Privacy Rule and exempt from HIPAA.

Deletion. Deletion is the removal, erasing, or expunging information or data from a record.

Disclosure. Disclosure is the release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity.

Health Information. Health Information is any information created or received by a health care provider or health plan that relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or payment for the provision of health care to an individual.

Identifiable Health Information. Identifiable Health Information is a subset of health information including demographic information collected from an individual.

Limited Data Set. Limited Data Set is protected health information that excludes specific direct identifiers of the individual or of relatives, employees or household members of an individual. A limited data set can only be used for the purposes of research, public health, or healthcare operations, and disclosed for the purpose of research.

Minimum Necessary. Minimum Necessary refers to the principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

Privacy Board. Privacy Board is the term used to describe a board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's private rights. Is an alternative to an IRB for privacy issues only; it cannot replace the IRB for Common Rule purposes.

Privacy Act. Privacy Act is an act that provides for the confidentiality of individually identified and retrieved information about living individuals that is maintained in a system of records and permits the disclosure of records only when specifically authorized by the statute. The Act provides that the collection of information about individuals is limited to that which is legally authorized, relevant, and necessary.

Privacy Rule. Privacy Rule provides guidance on the use of protected health information in the conduct of research. It imposes requirements on those involved in research, both individuals and institutions. Privacy refers to a person's desire to control the access of others to themselves. The evaluation of privacy involves consideration of how the investigator will access information from or about participants. The IRB members should know strategies to protect privacy interests relating to contact with potential participants, and access to private information.

Protected Health Information. Protected Health Information is individually identifiable health information transmitted or maintained electronically or in any other form or

medium, except for education records or employment records, as excluded in the Privacy Rule.

Preparatory Research. Preparatory Research is the method applied to developing or designing a research study.

Waiver of Authorization. Waiver of Authorization is a means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.

15.3 Historical Background

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. The resulting Privacy Rule, finalized in August 2002, set a compliance date of April 14, 2003. While the main impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research. Researchers, IRB staff and members as well as research administration must be aware of these changes.

15.4 Effects of HIPAA on Research

The final Privacy Rule published on August 14, 2002 included a number of changes in how the Rule applies to research. See the NIH HIPAA Privacy Rule Booklet for Research and the NIH fact sheet on Institutional Review Boards and HIPAA for more information on how HIPAA applies to research. See also *Impact of the Privacy Rule on Academic Research*, a white paper published by the American Council on Education.

The Privacy Rule does not make any changes to the Common Rule. However, it does contain several provisions that resemble provisions of the Common Rule and does make reference to those provisions. The Common Rule contains specific requirements for a composition of an IRB and the Privacy Rule contains specific requirements for a Privacy Board. The composition of a Privacy Board is similar to that of an IRB.

Connecticut Children's Medical Center is a covered entity under HIPAA. Researchers who are working with "Protected Health Information" (PHI) will be required to comply with the rules on HIPAA. The Connecticut Children's IRB acts as the Institution's Privacy Board.

The Privacy Rule permits covered entities to use or disclose protected health information for research purposes when the individual who is the subject of the information authorizes the use or disclosure. For clinical trials, authorization must be sought in addition to informed consent. Authorization must also be sought for other research uses or disclosures of protected health information that do not qualify for an IRB waiver of authorization (discussed below). The Privacy Rule has several special provisions that apply to research authorizations for uses and disclosures of PHI for research purposes. These requirements are as follows:

1. An authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues

until the end of the research study; and

2. An authorization for the use or disclosure of protected health information for research may be combined with a consent to participate in the research, or with any other legal permission related to the research study (except for research involving the use or disclosure of psychotherapy notes, which must be authorized separately); and
3. Research authorization forms must be filled out completely and accurately by the investigator, to ensure that all parties who require access to protected health information for the research (including sponsors, CROs, DSMBs, IRBs, etc.) are identified in the form and may receive the information. The IRB combined authorization/consent form should be completed by the investigator and submitted to the Connecticut Children's IRB for review and approval.

15.5 Research under HIPAA

HIPAA defines research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." This definition is identical with the one used in the "Common Rule", separate federal legislation designed to protect human subjects involved in research. HIPAA describes privacy standards for protecting PHI and so only applies to research that involves humans' (not animals') health information.

15.5.1 Waiver of Authorization for Use or Disclosure of Protected Health

Information in Research

Under the Privacy Rule, covered entities are permitted to use and disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances. A covered entity may use or disclose protected health information for research when presented with documentation that an IRB has granted a waiver of authorization [see 45 CFR 164.512(i)(1)(i)]. This provision of the Privacy Rule might be used, for example, to conduct records research, epidemiological studies, or other research where de-identified data is unavailable or not suited to the research purpose.

Investigators who wish to seek a waiver should submit the following documentation/information to the IRB:

1. Identification of the IRB or Privacy Board and the date on which the alteration or waiver of authorization was approved;
2. A statement that the IRB or Privacy Board has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
3. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or Privacy Board;
4. A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and

5. The signature of the chair or other member, as designated by the chair, of the IRB or the Privacy Board, as applicable.

The following criteria must be satisfied for the IRB to approve a waiver of authorization under the Privacy Rule:

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

1. an adequate plan to protect the identifiers from improper use and disclosure;
2. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
3. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
4. The research could not practicably be conducted without the waiver or alteration; and
5. The research could not practicably be conducted without access to and use of the protected health information.

15.5.2 Review Preparatory to Research

The Privacy Rule permits a covered entity to use or disclose protected health information to a researcher without authorization or waiver for the limited purpose of a “review preparatory to research.” Such reviews may be used to prepare a research protocol, to determine whether a research site has a sufficient population of potential research subjects, or for similar purposes preparatory to research such as to aid study recruitment (the researcher may identify, but not contact, potential participants) . Prior to permitting the researcher to access the protected health information, the covered entity must obtain representations from the researcher that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and that protected health information for which access is sought is necessary for the research purpose. Researchers should consult the covered entity regarding any forms or applications necessary to conduct a review preparatory to research.

Because the Privacy Rule permits a covered entity to disclose protected health information to the individual who is the subject of the information, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization. Even when permitted by the Privacy Rule, however, any use of patient information for recruitment must comply with IRB recruitment policies (see discussion below).

1. All human subjects' research requires IRB review to determine either a) exempt status or b) need for further review.
2. Reviews preparatory to research that are permitted under HIPAA may or may not be human subjects' research depending on the investigation being conducted.
 - a. Only those reviews of a database by an individual entitled to access that database intended to enumerate an available data set without reviewing PHI and for which no PHI is recorded do not require review. For example: medical records may be queried for information such as: In the year XXXX how many patients had a discharge diagnosis of [indicate disease/diagnosis]. IRB Privacy Board Review is required for all other uses of PHI as indicated.
 - b. If the research involves a de-identified data set, defined as removing the following identifiers, then a description of the de-identified data set (including a copy of the data collection tool where available) must be submitted for administrative review prior to accessing the data set. This activity also requires an IRB-determined exemption from review:
 1. Names
 2. Geographic info. (city, state, and zip)
 3. Elements of Dates (except years)
 4. Telephone #s
 5. Fax #s
 6. E-mail address
 7. Social Security#
 8. Medical Record, prescription #s
 9. Health Plan Beneficiary #s
 10. Account #s
 11. Certificate /License #s
 12. VIN and Serial #s, license plate #s.
 13. Device identifiers, serial #s
 14. Web URLs
 15. IP address #s
 16. Biometric identifiers (finger prints)
 17. Full face, comparable photo images
 18. Unique identifying #s

IRB Privacy Board review and approval is required prior to initiating this research. Investigators are not authorized to contact potential research subjects identified in reviews preparatory to research unless they are directly responsible for care of the potential subject and entitled to PHI as a result of that duty.

Investigators who have previously obtained full consent and authorization to contact a research subject as a result of a previously approved research project, may contact his or her former research subjects provided that the subject agreed to be contacted for information on future research conducted by the same principal investigator or co- investigator (s).

15.5.3 Research on Protected Health Information of Decedents

The protections of the Common Rule apply only to living human beings; by contrast, the Privacy Rule also protects the identifiable health information of deceased persons (“decedents”). The Privacy Rule contains an exception to the authorization requirement for research that involves the protected health information of decedents. A covered entity may use or disclose decedents’ protected health information for research if the entity obtains representations from the researcher that the use or disclosure being sought is solely for research on the protected health information of decedents, that the protected health information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought. Researchers should submit the applicable IRB form for IRB approval when they intend to conduct research involving decedents’ protected health information.

15.5.4 Limited Data Sets with a Data Use Agreement

When a researcher does not need direct identifiers for a study but does require certain data elements that are not permitted in de-identified data, the Privacy Rule permits a covered entity to disclose a “limited data set” to the researcher without authorization or waiver, provided that the researcher has signed a data use agreement. The limited data set is still considered to be protected health information, but it must exclude only specified direct identifiers of the individual or of relatives, employers, or household members of the individual.

A limited data set is defined as removing the following 16 identifiers:

1. Names
2. Postal address info. (if other than city, state and zip)
3. Telephone numbers
4. Fax numbers
5. Email addresses
6. Social Security #s
7. Medical record numbers
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vin and serial numbers, license plate numbers
12. Device identifiers, serial numbers
13. Web URLs
14. Internet protocol (IP) address numbers
15. Biometric identifiers including finger prints and voice prints
16. Full face photographic images and any comparable photo images

The Privacy Rule requires that the data use agreement used in conjunction with the limited data set contain provisions that:

1. Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not

include any use or disclosure that would violate the Rule if done by the covered entity;

2. Limit who can use or receive the data; and
3. Require the recipient to agree to the following:
 4. Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
 5. Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
 6. Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware; ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
 7. Not to identify the information or contact the individual;
 8. Researchers who will be receiving limited data sets must submit a signed copy of the covered entity's data use agreement to the IRB for approval, prior to initiating the research.

Transition Provisions

The Privacy Rule contains certain grandfathering provisions that permit a covered entity to use and disclose protected health information for research after the Rule's compliance date of April 14, 2003, if the researcher obtained any one of the following prior to the compliance date:

1. An authorization or other express legal permission from an individual to use or disclose protected health information for the research;
2. The informed consent of the individual to participate in the research; or
3. An IRB waiver of informed consent for the research.

Even if informed consent or other express legal permission was obtained prior to the compliance date, if new subjects are enrolled or existing subjects are re-consented after the compliance date, the covered entity must obtain the individual's authorization. For example, if there was a temporary waiver of informed consent for emergency research under the FDA's human subject protection regulations, and informed consent was later sought after the compliance date, individual authorization must be sought at the same time.

The transition provisions apply to both uses and disclosures of protected health information for specific research protocols and uses or disclosures to databases or repositories maintained for future research.

15.6 HIPAA and Documentation Requirements

HIPAA documents include an authorization form, a waiver of authorization form, and

a de-identification form. One of these documents must be used whenever PHI is utilized in the research.

15.7 Patient Rights and Research

Under HIPAA, patients have certain rights. Those that may affect research include the right to receive a Notice of Privacy Practices, the right to access, inspect, and receive a copy of one's own PHI, the right to request an amendment to one's own PHI, and the right to an accounting of certain disclosures of PHI that occur outside the scope of treatment, payment and health care operations that have not been authorized.

15.8 HIPAA and Existing Studies

Any research subject enrolled in a study that uses PHI from a covered entity must sign a HIPAA-compliant authorization form unless the IRB or Privacy Board approves a HIPAA waiver as described in Section 16.9. This form is in addition to the existing Informed Consent document, and is federally required. In a few cases, the Informed Consent document may be combined with a HIPAA authorization.

15.9 Waivers to HIPAA Consent Form

In some cases the IRB may approve a waiver to use of the HIPAA authorization form. This may occur when the IRB finds that the research could not be practically done without the waiver, and not without access to and use of the PHI, and that disclosure poses minimal risk to privacy.

16 Special Topics

16.1 Certificate of Confidentiality

Certificates of Confidentiality (CoC) are issued by the federal government to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. CoCs may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the subjects).

Any research project that collects personally identifiable, sensitive information and that has been approved by an IRB is eligible for a Certificate. Federal funding is not a

prerequisite for a Certificate.

16.1.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

16.1.2 Usage

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a Certificate of Confidentiality. Research can be considered "sensitive" if it involves the collection of:

1. information about sexual attitudes, preferences, practices;
2. information about personal use of alcohol, drugs, or other addictive products;
3. information about illegal conduct;
4. information that could damage an individual's financial standing, employability, or reputation within the community;
5. information in a subject's medical record that could lead to social stigmatization or discrimination; or
6. information about a subject's psychological well-being or mental health.

This list is not exhaustive. Researchers contemplating research on a topic that might qualify as sensitive should contact the IRB/HRPP Office for help in applying for a certificate.

In the informed consent form, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the

protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a Certificate is in effect.

16.1.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures.

For example, a Certificate does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if researchers intend to make such disclosures, this should be clearly stated in the informed consent form which research subjects are asked to sign.

In addition, a Certificate of Confidentiality does **not** authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if

1. the subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;
2. authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
3. release of such information is required by the Federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

16.1.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. For most research, Certificates are obtained from NIH. If NIH funds the research project, the NIH automatically grants the Certificate of Confidentiality. However, even if the research is not supported with NIH funding, the investigator may apply for a Certificate through the NIH.

If the research is conducting a sensitive research project that is covered by the AHRQ confidentiality statute (42 U.S.C. section 299a-1(c) entitled "limitation on use of certain information") or the Department of Justice confidentiality statute (42 USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (<http://grants.nih.gov/grants/policy/coc/index.htm>).

16.2 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including:

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed, such as mistaken paternity?
4. Does the subject or family member have the option not to know the results? How will this decision be recorded?
5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
7. Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

1. Will DNA be stored or shared? If shared, will the subject's identity be known by the new recipient investigator?
2. Will the subject be contacted in the future by the investigator to obtain updated clinical information?
3. How can the subject opt out of any distribution or subsequent use of his/her genetic material?

16.3 Research Involving Coded Private Information or Biological Specimens

Connecticut Children's policy is based on the OHRP guidance document entitled, **"Guidance on Research Involving Coded Private Information or Biological Specimens"** (dated October 16, 2008; available at:

<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
- Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subjects research.
- Provides guidance on who should determine whether human subjects are involved in research.

For purposes of this policy, *coded* means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been

replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human subject in Section 2 of this policy, *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means: (1) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any sources; and (2) using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human subjects if the following conditions are both met:

- (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; **and**
- (2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - (a) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
 - (b) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
 - (c) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects. Unless this human subjects' research is determined to be exempt, IRB review of the research would be required. Informed consent of the subjects also would be required unless

the IRB approved a waiver of informed consent.

16.3.1 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair, IRB Manager(s), or HRPP Director, will determine if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file.

16.4 Case Reports Requiring IRB Review

In general, an anecdotal report on a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and would not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians or reporting on greater than 3 cases, creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore would be considered research and would require IRB approval.

16.4.1 Definitions

Single Case Report: The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series: The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

16.5 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Connecticut law mandates that certain persons who suspect child or elder abuse or neglect report this to the Department of Children and Families or other appropriate state agency.

Connecticut Children's policy requires the solicitation of informed consent/parental permission and assent, as applicable, from all children and others involved as research subjects. In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect.

Mandatory reporting requirements are described in Connecticut Children's Organizational Policies, "Required Reporting to Public Agencies", and "Child Abuse and Neglect Reporting", available on the Connecticut Children's intranet.

Investigators should consider if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

16.6 Connecticut Children's Employees and Students as Subjects

When Connecticut Children's employees and/or students are being recruited as potential subjects, researchers must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Researchers must emphasize to subjects that neither their employment, nor academic status or grades, will be affected by their participation decision. Participation, including enrollment and ongoing research activities must remain completely private and research records must remain confidential.

The recruitment strategy must include additional safeguards; employees direct supervisors cannot be involved in the enrollment/consent process and cannot be informed of those employees who do or do not choose to voluntarily participate.

To minimize coercion, investigators should avoid, whenever possible, the use of their employees (ie direct reports or learners) when possible. Investigators should solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories **other than their own**. For example, if entering a classroom to recruit students and conduct research, e.g. administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

16.7 Student Research

16.7.1 Individual Research Projects Conducted by Students

Independent class projects, senior theses, undergraduate research projects, master's and advanced degree research, and similar exercises must be independently submitted for IRB review.

Connecticut Children's policy and procedures, educational training module information, forms and related information can be found on the IRB/HRPP website at: www.connecticutchildrens.org/research/human-research-protection-program/institutional-review-board/

16.7.2 Independent Study, Theses and Dissertations

These research activities are considered to meet the federal definition of human subjects' research and must be independently submitted to the IRB by the student-researcher. However, when students conduct research as part of a course of study, *a faculty member ultimately is responsible for the protection of the subjects*, even if the student is the primary researcher and actually directs the project. Advisers assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course. Students may serve as PIs, if they otherwise fulfill the PI eligibility criteria for the study and have a faculty sponsor who supervises the conduct of the research and serves as a co-investigator for the study.

16.8 Oral History

The following is based on guidance received from OHRP:

A decision whether oral history or other activities solely consisting of open ended qualitative type interviews are subject to the policies and regulations outlined in an institution's FWA and HHS regulations for the protection of human research subjects (45 CFR 46) is based on the prospective intent of the investigator and the definition of "research" under HHS regulations at 45 CFR 46.102(d): "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

General principles for evaluating Oral History type activities: 1) Oral history activities, such as open ended interviews, that ONLY document a specific historical event or the experiences of individuals without intent to draw conclusions or generalize findings would NOT constitute "research"; 2) Systematic investigations involving open-ended interviews that are designed to develop or contribute to generalizable knowledge (e.g., designed to draw conclusions, inform policy, or generalize findings) WOULD constitute "research"; 3) Creating an archive for the purpose of providing a resource for others to do research WOULD constitute research.

Investigators are advised to consult with the IRB Office regarding whether their oral history project requires IRB review.

16.9 Transnational Research

The IRB will review all transnational research utilizing human participants to assure adequate provisions are in place to protect the rights and welfare of the participants. All policies and procedures that are applied to research conducted domestically are applied to research conducted in other countries, as appropriate. For example, in the review and conduct of research, actions by Connecticut Children's will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the Belmont Report regardless of whether the research is conducted domestically or in other countries. Approval of research is permitted if the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46. Research conducted outside the United States by Connecticut Children's Medical Center investigators must also comply with the relevant laws of the host country.

16.9.1 Knowledge of Local Laws

The following procedures apply to transnational research to ensure knowledge of local laws for human research,

- The Connecticut Children's IRB must receive and review the foreign institution or site's IRB or EC (Ethics Committee) review and approval of each study prior to the commencement of the research at the foreign institution or site, when applicable. There are countries in which a local review board or government review mechanism is not available. In such cases, the research must be reviewed by an IRB member with expertise and knowledge of the country in which the research will be conducted or the Connecticut Children's IRB must obtain a consult from an individual who is familiar with the cultural background and local context of the country in which the research will be conducted. This individual may not be associated with the proposed research.
- The IRB staff conducting a pre-review of new applications for transnational research uses the current version of the United States Department of Health and Human Services Office for Human Research Protections (OHRP) "[International Compilation of Human Research Standards](#)" as a resource for identifying the host country's laws, regulations and guidelines for human research. This document is a listing of over 1,000 laws, regulations, and guidelines on human subjects' protections in over 100 countries and from several international organizations. The IRB staff will provide the IRB reviewer(s) with a list of the local laws, regulations and guidelines for human research and information on how to

access the laws, regulations and guidelines.

- For new protocols involving transnational research, the reviewer will assess the following questions in conducting expedited or full Board review.
 - Was the research approved by the foreign institution or site's IRB or EC and/or by the host country's government?
 - Was the research reviewed by an IRB member with expertise and knowledge of the country in which the research will be conducted or did the Connecticut Children's IRB obtain a consult from an individual who is familiar with the cultural background and local context of the country in which the research will be conducted? This individual may not be associated with the proposed research.
 - Does the research meet the requirements under the relevant laws, regulations and guidelines for the host country?

16.9.2 Knowledge of Local Research Context

The IRB will consider local research context when reviewing international studies to assure protections are in place that are appropriate to the setting in which the research will be conducted.

16.9.3 Qualifications of Researchers and Research Staff

The following procedures apply to transnational research to confirm the qualifications of the researchers and research staff for conducting research in that country:

- The review material must include adequate documentation to confirm the qualifications of the Connecticut Children's researchers and research staff to conduct research in the host country. Examples of documentation include relevant coursework, past experience, and training.
- The IRB will determine if there is adequate documentation regarding the qualifications of the researchers and research staff for conducting research in the host country. Documentation may include relevant coursework, experience, or training.

16.9.4 Continuing Review and Review of Modifications to Previously Approved Research

The following policies and procedures apply to continuing reviews of transnational

research and modifications to previously approved transnational research.

- The IRB is responsible for the ongoing review of transnational research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations. The continuing review process is described in Section 3.11 of this document.
- The IRB will require documentation of regular correspondence between the Connecticut Children's Investigator and the foreign institution or site and may require verification from sources other than the Connecticut Children's Investigator that there have been no substantial changes in the research since its last review.
- It is the responsibility of the Connecticut Children's Investigator to obtain IRB approval before making any changes in approved research unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified at once). The procedures for modifications are described in Section 3.12 of this document.
- It is the responsibility of the Connecticut Children's Investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research participants, etc.).

16.9.5 Handling of complaints, non-compliance, and unanticipated problems involving risks to participants or others

The Connecticut Children's investigator is responsible for reporting the following incidents to the Connecticut Children's IRB as described in Sections 8, 1 and 11 of this document: complaints; non-compliance; and unanticipated problems involving risks to participants or others. Oversight by the local IRB should include the handling of complaints, non-compliance, and unanticipated problems involving risks to participants or others. If there is no local IRB, Connecticut Children's IRB must fulfill these functions as described in Sections 8, 10 and 11 of this document.

16.9.6 Coordination and communication with local IRB or ECs when appropriate

The Connecticut Children's investigator is responsible for submitting the local IRB or EC approval documents and review material to the Connecticut Children's IRB. The Connecticut Children's investigator is also responsible for submitting copies of correspondence between the Connecticut Children's Investigator and the foreign institution or site to the Connecticut Children's IRB. The Connecticut Children's IRB may communicate directly with the local IRB or ECs when appropriate.

16.9.7 Additional Requirements

For Federally funded research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites “not engaged” in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the Investigator to conduct the proposed research at the site.
- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials are permitting the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/IEC determination, or letter of cooperation, as applicable.

The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the informed consent document. A translated consent form must be provided by the PI (if consent will be obtained in a language other than English), preferably a certified translation. If the translation is not certified, the PI should submit the name and qualifications of the person providing the translation, along with a back translation.

It is the responsibility of the Connecticut Children's Investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.

16.9.8 Monitoring of Approved Transnational Research:

The IRB is responsible for the ongoing review of transnational research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

The IRB will require documentation of regular correspondence between the Connecticut Children's Investigator and the foreign institution or site and may require verification from sources other than the Connecticut Children's Investigator that there have been no substantial changes in the research since its last review.

16.9.9 Independent Participating Transnational Research Sites

In some instances, a Connecticut Children's may be the PI and lead site for the overall study, but not be part of the research team conducting research at the participating foreign site. In these instances, the IRB application should indicate such, and the foreign site's IRB/EC or government would be responsible for oversight of all human subject research activities occurring at the foreign site. The Connecticut Children's PI should obtain documentation of the foreign participating site ethics committee's FWA and approval letter, and provide such documentation to the Connecticut Children's IRB.

The IRB is responsible for ultimately making the determination of whether a Connecticut Children's Investigator is involved in the conduct of the human subject research that is occurring at the foreign site, in accordance with the information provided in section 1.8 of this policy, 'Research Covered by the HRPP'.

Appendix A: Research involving Prisoners

Prisoners are another of the three classes that are deemed so vulnerable to exploitation in research that there are special rules protecting them. In the past, prisoners were viewed as a convenient research population. They are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, the conditions that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation.

The concern that Subpart C, and this policy based on Subpart C, attempt to address is whether prisoners have any real choice to participate in research, or whether incarceration prohibits free choice.

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies only to DHHS-funded research.

A.1 Applicability.

This policy applies to all biomedical and behavioral research conducted under the auspices of Connecticut Children's involving prisoners as subjects. Even though the IRB may approve a research protocol involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the Connecticut Department of Corrections and any other applicable State or local law. [45 CFR 46.301]

The research represents one of the following categories:

- o For DHHS-funded research, OHRP has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.
- o For DHHS-funded research which require the assignment of prisoners in a manner consistent with protocols approved by the

IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.

- o Epidemiologic studies that meet the following criteria:
 - Prisoners are not a particular focus of the research.

A.2 Minimal Risk

The definition of minimal risk that the IRB must use when reviewing research under Subpart C is different than in the rest of the federal regulations. According to 45 CFR 46.303, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Research involving prisoners can be reviewed by the expedited procedure using the following two options:

For research involving interaction with prisoners reviewed by the expedited procedure:

- Must be determined that the research involves no greater than minimal risk for the prison population being studied
 - o The prisoner representative must concur with the determination that the research involves no greater than minimal risk
- The prisoner representative must review the research as a reviewer, designated by the chair, or consultant. This may be as the sole reviewer or in addition to another reviewer, as appropriate.
- Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative.

For research that does not involve interaction with prisoners (e.g. existing data, record review) reviewed by the expedited procedure:

- A determination must be made that the research involves no greater than minimal risk for the prison population being studied
- Review by a prisoner representative is not required
- The prisoner representative may review the research as a reviewer or consultant if designated by the IRB chair.
- Review of modifications and continuing review must use the same procedures as initial review.

A.3 Composition of the IRB [45 CFR 46.304]

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB.
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy the requirements.
3. The prisoner representative must be a voting member of the IRB. The prisoner representative may be listed as an alternative member who becomes a voting member when needed.
4. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.
5. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer).
6. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
 - The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.
7. Continuing review and modifications involving more than a minor change must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

A.4 Additional Duties of the IRB [45 CFR 46.305]

In addition to all other responsibilities prescribed for the IRB in this manual regarding IRB review processes, the IRB will review research involving prisoners and approve such research only if it finds that:

1. The research falls into one of the following **permitted categories** [45 CFR 46.306]:
 - a. study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study

- presents no more than minimal risk and no more than inconvenience to the subjects;
 - b. study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - c. research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
 - d. research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.
2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
 3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
 4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
 5. The information is presented in language which is understandable to the subject population;
 6. Adequate assurance exists that the Parole Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
 7. Where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

A.5 When a Subject Becomes a Prisoner

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the IRB shall:

1. Confirm that the subject meets the definition of a prisoner.
2. Review the research study under Subpart C if it is feasible for the subject to remain in the study or require that the PI terminate the subject's enrollment.
 - If the temporary incarceration has no effect on the study, keep the participant enrolled.

- If the temporary incarceration has an effect on the study, handle according to the below guidance.
- 3. Before terminating the enrollment of the incarcerated subject, consider the risks associated with terminating participation in the study.
- 4. If the subject cannot be terminated for health or safety reasons,
 - i) Keep the subject enrolled in the study and will review the research under Subpart C. If some the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification; or
 - ii) Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.

A.6 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(I) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

(1) In which the sole purposes are:

- i. To describe the prevalence or incidence of a disease by identifying all cases, or
- ii. To study potential risk factor associations for a disease, and 46.305(a)(2)–(7) and determined and documented that
- iii. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
- iv. Prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR 46.306(a)(2).

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects.

In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data.

Appendix B: Department of Defense (DoD)-Funded Research

Research conducted or supported by the Department of Defense (DoD), including the separate components, or recruitment of DoD personnel requires compliance with additional federal regulations, directives and instructions. This Appendix applies to human subject research that is funded by any DOD component or that specifically recruits participants from the DoD.

B. 1 Definitions

Research involving a human being as an experimental subject: An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of section 980 of Sections 139(a)(2)(A), 980, 1074f , and 1102 of title 10, United States Code; it does not affect the application of part 219 of Parts 22 (Appendix B), 37 (Appendix D), 108 and 2191 of title 32, Code of Federal Regulations. This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

Minimal Risk: the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests in normal persons” shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

Research Monitor: a physician, dentist, psychologist, nurse, or other healthcare provider capable of overseeing the progress of the research protocol, especially issues of individual subject/patient management and safety.

B.2 Specific Considerations

Scientific Review

The DoD requires scientific review prior to IRB review for all new DoD supported human research. In addition, DoD requires that all substantive amendments receive scientific review prior to IRB review. Therefore, the Scientific Review Committee (SRC) will review all new studies and substantive amendments that receive DoD support.

Education Requirements

All personnel who conduct, review, approve, oversee, support, or manage human participants research that is DoD-funded are required to meet the DoD research ethics training requirements. Before the PI receives IRB approval documentation for DoD-funded research, the HRPP staff will confirm that all personnel who conduct the research completed the DoD-required research ethics training.

Greater than Minimal Risk Studies: Research Monitor Required

The IRB must confirm that the following have been met:

- ☐ An independent research monitor has been appointed by name
- ☐ The research monitor must be independent of the team conducting the research
- ☐ The research monitor has the authority to stop a research study in progress, remove individuals from a research study, and take any steps to protect the safety and well-being of participants until the IRB can make an assessment
- ☐ The research monitor possesses sufficient educational and professional experience to serve as the subject advocate
- ☐ A written summary of the monitor's duties, authorities, and responsibilities has been provided to the IRB and is appropriate
 - ☐ The duties of the research monitor are determined on the basis of specific risks or concerns about the research.

Vulnerable Populations

Research involving pregnant women, prisoners, and children that is conducted or supported by the DoD is subject to the DHHS Subparts, B, C, and D. In addition, the DoD has supplemental requirements for research involving these populations.

Involvement of Pregnant Women, Fetuses, and Neonates

- ☐ For the purposes of applying Subpart B, the phrase “biomedical knowledge” shall be replaced with “generalizable knowledge.”
- ☐ The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- ☐ Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g on the transplantation of fetal tissue.

Involvement of Prisoners

- ☐ Research involving prisoners cannot be reviewed by the expedited procedure
- ☐ When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum
- ☐ In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
 - i) The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - ii) The research presents no more than minimal risk.
 - iii) The research presents no more than an inconvenience to the participant.
- ☐ The guidelines for when a participant becomes a prisoner are consistent with the guidelines that the Connecticut Children's IRB follows, as set forth in Appendix A.
- ☐ Research involving a detainee as a human participants is prohibited.

- o This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.
- ❑ Research involving prisoners of war is prohibited.

Involvement of Children

- ❑ The exemption for research involving survey or interview procedures or observation of public behavior does not apply to research with children except for research involving observation of public behavior when the investigators do not participate in the activities being observed. The Connecticut Children's IRB has the same requirement.

Classified Research

Non-exempt classified research must be conducted following the requirements of 3216.02.13.

Additional Protections for Military Personnel

U.S. military personnel may not be involved in DOD funded research unless the following protections are included to minimize undue influence:

- ❑ Officers are not permitted to influence the decision of their subordinates.
- ❑ Officers and senior non-commissioned officers may not be present at the time of recruitment
- ❑ Officers and senior non-commissioned officers have a separate opportunity to participate.
- ❑ When recruitment involves a percentage of a unit, an independent ombudsman is present.

When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:

- ❑ Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- ❑ Non-Federal persons may be compensated for research participation other than blood draws in reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

Informed Consent Process

Disclosure of Research-Related Injury

- ❑ The PI is responsible for informing the IRB if there are any requirements from the DoD component regarding the provision of care for a research-related injury. These requirements also require disclosure in the informed consent document.

Consent from a Legally Authorized Representative

- ❑ If consent is to be obtained from the legally authorized representative of an experimental subject, the research must be intended to provide direct benefit to the

individual participant. The determination that the research is beneficial to the individual experimental subject must first be made by the IRB.

Limitations on Waiver of Consent

The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when the following have been met:

- ☐ The research is necessary to advance the development of a medical product for the Military Services
- ☐ The research may directly benefit the individual experimental subject
- ☐ The research is conducted in compliance with all other applicable laws and regulations.

The IRB may waive the requirements for consent when:

- ☐ The research participant being considered does not meet the definition of an experimental subject.'
- ☐ DoD regulations prohibit an exception from informed consent in emergency medicine research unless a waiver is obtained from the Secretary of Defense.

Additional Investigator Responsibilities

Any surveys performed on Department of Defense personnel must be submitted, reviewed and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.

In addition, within 30 days, the investigator must report the following to the DOD human research protection officer:

- Significant changes to the research protocol approved by the IRB.
- The results of the IRB continuing review.
- Change of reviewing IRB.
- When Connecticut Children's is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

If a Connecticut Children's investigator is the lead investigator for a multi-centered study, an agreement or statement of work with all collaborating sites that delineates each site's responsibilities must be executed. The document should include the following:

- A brief description of the research
- Specific roles and responsibilities of each site, including scientific and IRB review; recruitment of participants, and informed consent procedures
- Plan for ongoing data and safety monitoring, reporting requirements, documentation retention, and compliance for the entire research project

International Research

If research will be conducted with international populations, the following additional safeguards must be in place:

- ❑ Connecticut Children's or the researcher has permission to conduct research in that country by certification or local ethics review
- ❑ The investigator follows all local laws, regulations, customs, and practices.

Appendix C: Research Conducted in Schools

This policy applies to all research conducted in school settings where the Connecticut Children's IRB serves as the Reviewing IRB.

All human subjects research that is to be conducted with Department of Education (DoE) funding or that takes place in a school setting must be submitted and reviewed in accordance with the Connecticut Children's HRPP Standard Operating Procedures. In addition to the federal research regulations and Connecticut Children's HRPP SOPs, the investigators must also comply with the requirements of the Protection of Pupil Rights Amendment (PPRA, 20 U.S.C. § 1232h; 34 CFR Part 98) which is part of the No Child Left Behind Act of 2001(Public Law 107110) and the Family Educational Rights and Privacy Act (FERPA (20 U.S.C. § 1232g; 34 CFR Part 99), when applicable.

Definitions:

Consent: For the purposes of this appendix, consent includes parental permission and student consent, when permitted under state law.

DoE: Department of Education.

FERPA (Family Educational Rights and Privacy Act): A Federal law that protects the privacy of student education records. In general, schools must have written permission from the parent or eligible student in order to release any information from a student's education record.

PPRA (Protection of Pupil Rights Amendment): Federal regulation which is part of the No Child Left Behind Act of 2001(Public Law 107-110) which specifies eight categories of protected information in surveys of minors in schools. There are two sets of requirements for surveys applying to protected information: for surveys funded by the US DOE and are funded by sources other than the U.S. Department of Education and that are administered or distributed by education institutions that receive funds from any Department of Education program (i.e., public elementary and secondary schools and some private schools).

Procedures:

A. Review of research conducted in a school setting

All human subjects research that will be conducted in a school setting must be submitted and reviewed in accordance with the Connecticut Children's HRPP SOPs. The IRB may determine that the research meets the criteria for exemption or that it requires review and approval by either expedited procedures or the convened board.

B. Approval by the school or school district

The investigator must obtain approval notification or written documentation of support from the authorized individual(s) within the school or school district where the research will take place prior to initiating study activities within the school. Investigators must comply with each school's applicable policies when conducting the research.

C. School engagement in human subjects research

If agents of the school are engaged in human subjects research as defined by OHRP's 2008 Guidance on Engagement in Human Subjects Research, the school must either:

- (i) obtain approval/exemption determination from their own IRB and privacy board review (when applicable), or
- (ii) the school must sign an agreement to work under the jurisdiction of Connecticut Children's IRB.

Schools that are only used as a site for research and permit Connecticut Children's investigators to perform all the research procedures, including recruitment and obtaining consent would not be considered engaged in research.

D. Ensuring Adherence to FERPA Requirements

FERPA protects the privacy of student education records. Schools must have written permission from the parent or eligible student in order to release any information from a student's education record. However, FERPA allows schools to disclose personally identifiable information from an education record of a student without consent if the disclosure is to organizations conducting studies for, or on behalf of, educational agencies or institutions to develop, validate, or administer predictive tests; administer student aid programs; or improve instruction.

(i) Exception to Written Permission for Records Release under FERPA

Requests for exception (waiver) to consent for student education records release are reviewed by the Connecticut Children's IRB. A school district or postsecondary institution that uses this exception is required to enter into a written agreement with Connecticut Children's or with the investigator conducting the research that specifies:

The determination of the exception.

Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

- (1) Student's name and other direct personal identifiers, such as the student's social security number or student number.
- (2) Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable, date and place of birth, and mother's maiden name.
- (3) Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence,

- facial characteristics, and handwriting.
- (5) Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

The purpose, scope, and duration of the study

- (1) That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in 34 CFR 99.31(a)(6) on re-disclosure and destruction of information.
- (2) That Connecticut Children's/the Investigator is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study.
- (3) The time period during which Connecticut Children's/the Investigator must either destroy or return the information.
- (4) The information to be disclosed.
- (5) That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the university with legitimate interests. For research accessing educational institution student records without consent, the responsibility for complying with FERPA-specific consent exception requirements, including requirements for removal of all personally identifiable information, will be the responsibility of the investigator in conjunction with the educational institution.

E. Ensuring Adherence to PPRA Requirements

The PPRA gives parents rights with respect to surveying minor students, the collection, disclosure or use of information. Under this law no student shall be required, as part of any research project, to submit without consent to protected information surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment. Protected information includes the following categories:

- (1) political affiliations of student or student's parent;
- (2) mental or psychological problems of student or student's family;
- (3) sex behavior or attitudes;
- (4) illegal, anti-social, self-incriminating or demeaning behavior;
- (5) critical appraisals of others with whom students have close family relationships;
- (6) legally recognized privileged or analogous relationships (such as those of lawyers, physicians and ministers);
- (7) religious practices, affiliations or beliefs of student or student's parent;
- (8) income.

PPRA also requires local educational agencies to notify parents of the policies and to offer parents the opportunity to opt out of (remove child from) participation in third-party surveys involving protected information. These requirements suggest that local schools have the discretion to set up their own individual policies for non-US Department of Education protected information surveys.

Appendix D: Research Subject to Environmental Protection Agency (EPA) Requirements

In addition to the above noted requirements in section 6.6.1.2, the following apply to EPA-supported research:

1. Research involving the intentional exposure of pregnant women, nursing women, or children to any substance is prohibited.
2. 40 CFR 26 Subparts C and D will be applied to provide additional protections to pregnant women and children as participants in observational research (research that does not involve intentional exposure to any substance).
3. IRB determinations and approval will be submitted to the EPA research involving human participants review official for final review and approval before the research can begin.
4. For research not conducted or supported by any federal agency that has regulations for protecting human research participants and for which the intention of the research is submission to the EPA, the EPA regulations protecting human research participants apply, including:
 - o EPA extends the provisions of the 40 CFR 26 to human research involving the intentional exposure of non-pregnant, non-nursing adults to any substance.
 - o EPA prohibits the intentional exposure of pregnant women, nursing women, or children to any substance.

Appendix E: Planned Emergency Research

For planned emergency research, the convened IRB with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must find and document each of the following:

- The research activity is subject to the FDA regulations 21 CFR 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE).
- The application clearly identifies the protocols that will include participants who are unable to consent.
- The research participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which might include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining consent is not feasible because:
 - o The participants will not be able to give their consent as a result of their medical condition.
 - o The intervention under investigation may need to be administered before consent from the participants' legally authorized representatives is feasible.
 - o There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- Participation in the research holds out the prospect of direct benefit to the participants because:
 - o Participants are facing a life-threatening situation that necessitates intervention.
 - o Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the individual participants.
 - o Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what was known about the risks and benefits of the proposed intervention or activity.
- The clinical investigation cannot practicably be carried out without the waiver.
- The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each participant within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent.
 - o The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the convened IRB at

- the time of continuing review.
- The convened IRB will review and approve consent procedures and a consent document consistent with 50.25. These procedures and the consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documents was feasible.
 - o The convened IRB will review and approve procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the clinical investigation consistent with the paragraph below.
 - Additional protections of the rights and welfare of the participants will be provided, including, at least:
 - o Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the participants will be drawn.
 - o Public disclosure to the communities in which the clinical investigation will be conducted and from which the participants will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.
 - o Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.
 - o Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.
 - o If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the investigator commits, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a legally authorized representative, and asking whether he or she objects to the participant's participation in the clinical investigation.
 - The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
 - Procedures are in place to inform, at the earliest feasible opportunity, each participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, of the participant's inclusion in the clinical investigation, the details of the investigation and other information contained in the consent document.
 - There is a procedure to inform the participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, that he or she might discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

- If a legally authorized representative or family member is told about the clinical investigation and the participant's condition improves, the participant is also to be informed as soon as feasible.
- If a participant is entered into a clinical investigation with waived consent and the participant dies before a legally authorized representative or a family member can be contacted, information about the clinical investigation is to be provided to the participant's legally authorized representative or family member, if feasible.
- The protocol is performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identified such protocols as protocols that might include participants who were unable to consent.
 - The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.
 - If an IRB determines that it could not approve a clinical investigation because the investigation did not meet the criteria in the exception or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly (no longer than within 30 days) in writing to the clinical investigator and to the sponsor of the clinical investigation.

Research not subject to FDA regulations:

- The IRB must find, document, and report to DHHS that the following conditions have been met relative to the research.
- The IRB finds and documents that the research is not subject to regulations codified by the FDA 21 CFR 50.
- The research participants are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which might include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- Obtaining consent is not feasible because:
 - o The participants are not able to give their consent as a result of their medical condition.
 - o The intervention involved in the research is administered before consent from the participants' legally authorized representatives is feasible.
 - o There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
- Participation in the research holds out the prospect of direct benefit to the participants because:
 - o Participants are facing a life-threatening situation that necessitates intervention.
 - o Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence supported the potential for the intervention to provide a direct benefit to the

individual participants.

- o The risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of participants, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The research cannot practicably be carried out without the waiver.
- The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each participant within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.
- The convened IRB must review and approve consent procedures and a consent document in accord with 45 CFR 46.116 and 46.117.
 - o These procedures and the consent document are to be used with participants or their legally authorized representatives in situations where use of such procedures and documents is feasible.
 - o The convened IRB must review and approve procedures and information to be used when providing an opportunity for a family member to object to a participant's participation in the research consistent with the paragraph of this waiver.
- Additional protections of the rights and welfare of the participants are provided, including, at least:
 - o Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research is conducted and from which the participants are drawn.
 - o Public disclosure to the communities in which the research is conducted and from which the participants are drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits.
 - o Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.
 - o Establishment of an independent data monitoring committee to exercise oversight of the research.
 - o If obtaining consent is not feasible and a legally authorized representative is not reasonably available, the investigator commits, if feasible, to attempting to contact within the therapeutic window the participant's family member who is not a legally authorized representative, and asking whether he or she objected to the participant's participation in the research.

- The investigator must summarize efforts made to contact family members and make this information available to the convened IRB at the time of continuing review.
- Procedures are in place to inform, at the earliest feasible opportunity, each participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, of the participant's inclusion in the research, the details of the research and other information contained in the consent document.
- There is a procedure to inform the participant, or if the participant remains incapacitated, a legally authorized representative of the participant, or if such a representative is not reasonably available, a family member, that he or she can discontinue the participant's participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
- If a legally authorized representative or family member is told about the research and the participant's condition improves, the participant is also informed as soon as feasible.
- If a participant is entered into research with waived consent and the participant dies before a legally authorized representative or family member can be contacted, information about the research is provided to the participant's legally authorized representative or family member, if feasible.
- For the purposes of this waiver "family member" means any one of the following legally competent persons: spouses; parents; children including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the participant was the equivalent of a family relationship.

Appendix F: HRPP Emergency Preparedness Plan

Overview

The HRPP is committed to implementing policies and procedures that will ensure the safety and welfare of research participants during an emergency/disaster scenario. The HRPP consists of individuals, administrative units, and committees with responsibilities for human research protection. The HRPP Emergency Preparedness Plan establishes IRB specific emergency planning and is intended to supplement, not replace, emergency response planning by Institutional leadership and/or Institution-wide response measures.

The Institution and the HRPP routinely assess potential emergency scenarios and threats to the institution to improve its emergency preparedness and response plan. The emergency preparedness and response plan will be followed when a situation impacting the HRPP has occurred, or in preparation for scenarios where a potential emergency situation is imminent such as:

1. Extreme weather events
2. Natural disasters
3. Man-made disasters
4. Infectious disease outbreaks
5. IT issues including IT failures and cyber threats

Institutional Responsibilities

The Institution has an Emergency Management Program which guides the hospital's approach to responding to emergencies within the organization and/or the community that would suddenly and significantly affect the need for the hospital's services and its ability to provide those services, and pose an immediate or potential danger to the health and safety of patients, staff and visitors. The program is also designed for compliance with applicable codes and regulations. The program is applied to Connecticut Children's and all off-site locations. The plan is reviewed annually by the Hospital Emergency Operations Plan (HEOP). Additional information and details can be found in the [Hospital Emergency Operations Plan Policy](#).

HRPP Responsibilities

The HRPP emergency preparedness plan focuses on continuity of HRPP/IRB operations in the event of an emergency that could impede normal business operations and the research conducted at sites under the jurisdiction of the Connecticut Children's IRB as well as external research sites for which Connecticut Children's is designated as the Reviewing IRB under a reliance agreement/arrangement.

In the event of an emergency, HRPP/IRB leadership will work with the Institutional Official (IO) and other Institutional leadership to implement appropriate emergency response procedures for oversight and conduct of human subject research that align with the

Institution's overall emergency response.

Research Team Responsibilities

Researchers should consider the need for an emergency response plan. Emergencies can lead to difficulty with conducting study procedures, safety monitoring, communications with participants and access to and use of investigational drugs and devices. The complexity of the emergency response plan should be driven by the type of emergency, type of study and the associated risks.

1. As a first step, the researcher should determine if an emergency response plan is necessary. A plan may not be needed if the research does not involve in-person interactions, or the research can be conducted as approved by the IRB while adhering to institutional requirements regarding the emergency.
2. When studies have an external sponsor, the researcher must contact the sponsor to determine if they have an emergency response plan in place.
3. Any institutional requirements that are more restrictive than a sponsor's emergency response plan must be followed.
4. Emergency response plans should take into consideration all locations where the research is conducted, such as the hospital, community, or other external location.
5. Plans to conduct research at alternate locations in response to the emergency will require prospective IRB approval.

The need for a potential response plan is based on the type of research conducted and degree of risk in the event the study could not continue; please see the below section titled Investigator Considerations for more detailed considerations.

HRPP/IRB Staffing Levels

The HRPP/IRB staff are sufficiently prepared to work in a remote environment, including staff who are working outside of the immediate Hartford area. As a result, the impact of specific threats and hazards are somewhat mitigated by the dispersed nature of support personnel. It is anticipated that enough staff will be available at any given time to process emergency submissions as needed. HRPP/IRB leadership will assess staffing availability throughout the duration of an emergency situation to ensure urgent IRB needs are met. For individual HRPP staff members whose work functions are limited or disrupted due to utility, communication, or IT outages, the staff member will contact the IRB Manager, HRPP Director(s) or designated back-up personnel. Required work will be re-directed to an IRB staff member who is not impacted, with access to necessary HRPP resources and systems.

Electronic Systems

All data on Connecticut Children's servers are backed up and resides in the data centers. Backed up data is replicated to each data center location on a daily basis as a minimum for disaster recovery.

The electronic systems supporting the functions under the HRPP are hosted by OneAegis (also known as IRBManager), which delivers a robust, secure, and performant hosted solution to managing all research compliance needs. The primary data center is Amazon Web Services (AWS) GovCloud's US-Gov-West-1 region, with a multiple availability-zone deployment to mitigate the impact of any disaster. A warm standby is maintained in case of a region-wide AWS failure. Details of AWS's security compliance and certifications is available online at <https://aws.amazon.com/compliance/programs/>.

Recovery Backups are automated with full backups performed daily and transaction-log backups every 5 minutes, in addition to synchronous mirroring of the databases between two availability zones. Backups are immediately sent to encrypted AWS S3 buckets. Backups are automatically applied on secondary servers to confirm the backup is sound and complete. In addition to the restored warm-standby copy, individual backups are kept for 270 days, although shorter time-limits are available upon request.

In the event that the electronic system is unavailable, the HRPP will implement alternative measures to receive time critical IRB submissions for review.

IRB Committee Functions

IRB meetings are held virtually using a Zoom platform. As a result, it is anticipated that IRB meetings will be able to continue even if members must shelter in place. In the event the Zoom platform is unavailable, a teleconference will be scheduled. In instances where the convened IRB is unable to meet or quorum cannot be obtained and IRB approval for a study may lapse, the IRB Chair can determine whether subjects can continue to participate in research activities if it is in the best interest of already enrolled subjects. Should an emergency be ongoing and IRB quorum cannot be obtained, HRPP/IRB leadership will assess options for transferring IRB oversight to an external, independent IRB. Preference will be given to IRBs that hold AAHRPP accreditation and are a SMART IRB Agreement participating institution.

Responses to Emergency

In the event that an emergency necessitates limitations on the conduct of human subject research, the Institution will implement a risk-based approach to determining how and when research with human subjects may continue. Research will be categorized by risk level, and risk levels will correspond to overall Institution-wide research operations. In emergencies caused by potential viral transmission, the Institution will provide a matrix of which studies can continue based on risk incurred by the continuation of the study.

An evaluation will be performed to determine whether the nature of the emergency/disaster may pose additional threats or risk to specific aspects of the institutions research activities or facilities (e.g., man-made disasters, industrial accidents, or terrorist threats could potentially impact some chemical, biological, or radiologic facilities to a greater extent than other facilities.). If yes, and if broader institution-level emergency/disaster preparedness measures do not already address these specific activities or facilities, HRPP leadership will work with the IO and appropriate institutional

leadership to escalate and address any additional threats or risks.

The nature of each emergency will dictate the specific response taken by the HRPP leadership. Response actions may include:

- **Triaging the research that will be subject to the emergency mitigation strategies:** Consideration will be given to types of research that may continue and the types of research that may need to be temporarily postponed. This consideration may include:
 - Permitting studies which present a likelihood of direct benefit to participants or those where discontinuation of the study interventions may be harmful to participants
 - Postponing studies which may have an adverse impact on resources required to address the emergency
- **Postponing new study implementation:** Consider not accepting submissions of new protocols for IRB review for research which is non-interventional in nature, or which presents no direct benefit to participants.
- **Suspending enrollment of existing research:** The IRB may need to identify studies for which recruitment and/or enrollment should be suspended, but ongoing study interventions may continue.
- **Continuing studies via alternate mechanisms:** When possible, implement online or remote strategies for research procedures such as recruitment, consent, data collection, debriefing, and follow-up. Identify any additional research activities that can be completed via telephone, video conference, or via online mechanisms. If possible, alter the timing of visits and procedures.
- **Implementing flexibilities for non-federally funded research:** When studies are not federally regulated, organizations may employ different but equivalent procedures in terms of protecting the rights and welfare of research participants. For example, extension of continuing review dates or eliminating the need for prospective IRB review for minor procedural changes necessitated by the emergency.
- **Relying on another organization to provide IRB oversight:** In the event the Connecticut Children's IRB is not able to complete IRB review functions, reliance on other IRBs may serve as an alternative to an internal IRB review process. HRPP/IRB will leverage their standard operating procedures that are currently in place for reliance activities. This includes reliance on commercial IRBs, or other independent IRBs with preference to those that are a member of the SMART IRB initiative and AAHRPP accredited.
- **Considering more widespread use of waivers of documentation** of informed consent for most minimal risk research that involves interaction with participants.

Training

HRPP leadership will coordinate with organizational officials in the development and implementation of training materials related to emergency preparedness and response plans specific to human research conducted at the organization. The HRPP emergency preparedness plan will be made available to the human research community via the

HRPP intranet website. The organization is responsible for notifying research teams when the organization's emergency response plan is activated. The IRB members and HRPP staff will periodically be provided with information and training about the HRPP emergency plan. The information provided will be reassessed periodically to ensure it aligns with the Institutional emergency operations plan and the HRPP emergency plan.

Communication

In the event the emergency plan needs to be implemented, information will be distributed to the research community from the HRPP Medical Director, HRPP Director, or Institutional Official. These plans will also be disseminated to the research community through the HRPP intranet website.

When the emergency/disaster no longer presents a limitation to human subject research activities, HRPP leadership will work with the IO to notify the research community that normal business operations have resumed.

Investigator Considerations

The need for a response plan is based on the type of research conducted and degree of risk in the event the study could not continue. The plan should address if specific treatments or assessments need to be interrupted/delayed/changed and whether follow up visits and assessments may be performed remotely or in other locations.

Investigators need to have emergency response plans contemplated for the types of research they perform, and the location utilized for research. This will be dependent on whether the research or components of the research are conducted at the hospital (inpatient or outpatient), in the community or remotely.

Changes made to the conduct of the research protocol, safety management plans, etc require submission of an amendment and IRB approval prior to implementation, with the exception of changes to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to the subject or others, which requires a Reportable New Information submission. Investigators are encouraged to consider incorporating the following into their emergency response plans:

- **Alternative approaches to safety monitoring and obtaining consent:**
 - **Safety monitoring:** Investigators may develop alternative mechanisms for safety monitoring. If trial participants may not be able to come to the investigational site for protocol specified visits, the IRB will evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible and would be sufficient to assure the safety of trial participants.
 - **Consenting procedures:** In some studies, Investigators may ask the IRB for a waiver of informed consent documentation during a disaster or emergency. The IRB has guidance for remote and electronic consent, and

this may be utilized in the event of an emergency or disaster when it is not possible to get in person consent or when new information needs to be presented to those who have already provided written consent.

- **Emergency contact information:** Collect and update participants' emergency contact information annually if their health, safety, or welfare could be jeopardized during an emergency. Investigators must be able to access/retrieve this information under emergency conditions (for example, if computer systems are down).
- **Organization wide changes:** If there are institution-wide changes that impact clinical care and research in similar ways, these changes do not require IRB review. Examples of changes that do not require IRB review include screening procedures mandated by the health care system in which a protocol is being conducted.