

Texas Health Resources



Corporate Policy for Protection of Human Research Subjects

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Revisions Table

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Tanya Poe, Research Compliance Director	Research Activities Compliance Committee (RACC)	THR System Performance Council (SPC)	12 February 2008	12 February 2008	
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Heather Cline, MPA, CIP, IRB Manager & Research Compliance Officer	RACC	SLC	16 February 2016	11 March 2016	<i>New Section 16 added:</i> Research Misconduct: Allegations, Investigations, and Reporting
Heather Cline, MPA, CIP, IRB Manager & Research Compliance Officer	RACC	Not applicable	09 March 2016	25 March 2016	<i>Section 4-3-</i> clarification on who May Serve as the Principal Investigator at THR <i>Section 5-8-</i> clarification on

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

					<p>studies that involve transfer of genetic information collected as part of standard of care to a Sponsor for research purposes eligibility for external IRB</p> <p><u>Section 5-9</u>-new section, Conflict of Interest Review for Studies Relying on an External IRB</p> <p><u>Section 12-12</u>-clarification that HUD submissions do not require Conflict of Interest disclosure</p>
Heather Cline, MPA, CIP, IRB Manager & Research Compliance Officer	RACC	Not applicable	13 April 2016	22 April 2016	<p><u>Section 5-1 to 5-2</u>- Updates to language to clarify fee exemption approvals and to remove procedural/process language that should be an SOP vs. a policy.</p> <p><u>Section 9-22</u>- Updates to the policy for administrative closures. RACC will be notified as well as the Entity Reviewer and Chief Medical Officer at the THR facility where the research is conducted.</p>

Table of Contents

Chapters

1. The Ethical Mandate to Protect Human Subjects	
a. The Nuremberg Code.....	1-1
b. The Declaration of Helsinki	1-1
c. The Belmont Report	1-1
2. The Regulatory Mandate to Protect Human Subjects	
a. Department of Health and Human Services (DHHS) Regulations	2-1
b. Food and Drug Administration (FDA) Regulations	2-1
c. The Assurance and IRB Registration Process	2-1
<i>THR Agent Defined</i>	2-2
<i>Coverage Under the THR FWA</i>	2-2
<i>Operation of THR IRB</i>	2-2
d. THR Policies	2-2
3. Types of Human Subject Research	
a. Definition of Human Subject and Research	3-1
<i>Research Defined</i>	3-1
<i>Systematic Investigation Defined</i>	3-1
<i>Generalizable Knowledge Defined</i>	3-1
<i>Research or Clinical Investigation Defined</i>	3-1
<i>Human Subject Defined</i>	3-1
<i>Private Information Defined</i>	3-1
<i>Identifiable Defined</i>	3-2
b. Level of Risk Defined	3-2
<i>Minimal Risk Defined</i>	3-2
<i>Minimal Risk for Prisoners</i>	3-2
c. Types of Human Subject Research	3-2
<i>Biomedical Research</i>	3-2
<i>Social and Behavioral Research</i>	3-2
<i>Clinical Research</i>	3-2
<i>Epidemiology Research</i>	3-2
<i>Repository Research</i>	3-3
<i>Pilot Studies</i>	3-3
d. Quality Improvement (QI) Activities as Human Subject Research	3-3
e. Research Activities versus Commercial Services	3-4
f. Engagement Defined	3-5

4. Shared Responsibilities for Protecting Human Subjects

a.	THR Institutional Responsibilities.....	4-1
	<i>THR Board of Trustees</i>	4-1
	<i>THR Institutional Official</i>	4-1
b.	The Institutional Review Board (IRB)	4-2
c.	The Principal Investigator	4-2
	<i>Principal Investigators' Responsibilities</i>	4-3
	<i>Notice of Inspection From Regulatory Authorities</i>	4-3
	<i>Changes to Approved Research</i>	4-3
	<i>Adverse Events/Notice of Unanticipated Problems</i>	4-4
	<i>Notice of Completion, Discontinuance of Project or Withdrawal of Exemption</i>	4-4
	<i>Subsequent Use of Data from Closed Research</i>	4-6
	<i>Investigator Records</i>	4-5
	<i>Hospital Affiliation</i>	4-7
d.	Other Members of the Research Team	4-7
e.	Research Subjects	4-7
	<i>Subjects' Right to Withdraw</i>	4-8

5. Institutional Review Board (IRB) Roles and Authorities

a.	Human Subject Protections under Federal Regulations	5-1
	<i>THR Federal-wide Assurance and Registration of THR IRB</i>	5-1
b.	Corporate Authority and Oversight of THR IRBs	5-1
	<i>IRB Review Fees</i>	5-1
c.	Purpose of the IRB	5-2
d.	Scope of the IRB's Authority	5-3
	<i>Approval of THR Entity Where Research Will Be Conducted</i> ...	5-3
	<i>Requirement for Prospective Review and Approval</i>	5-3
	<i>Adding a New Site to an Existing Approved Protocol</i>	5-3
	<i>Independent Conduct of the Same Research at Two THR Sites</i>	5-3
	<i>Power to Take Action</i>	5-4
	<i>Power to Suspend or Terminate Enrollment</i>	5-4
	<i>Cases of Serious or Continuing Noncompliance</i>	5-4
e.	Appeal of IRB Determinations	5-4
	<i>No Set Aside or Overrule Permitted</i>	5-4
	<i>Notice to Investigator</i>	5-4
	<i>Investigator Response and Appeal</i>	5-5
f.	Other THR IRB Responsibilities	5-4
g.	Responsibilities to Regulatory Agencies	5-5

h.	THR IRB Review of Non-THR Research	5-6
i.	Relationship of the IRB to Other Institutions	5-6
j.	Human Subject Protection Education Program	5-6
k.	Relationship of the IRB to IND/IDE Sponsors	5-6
l.	Compliance Review and Oversight of Human Protection Activities	5-7
m.	Privacy Board Functions and Determinations	5-7
n.	Reliance on the IRB of Another Institution, Organization, or an Independent (Commercial) IRB	5-7
6.	IRB Structure and Membership	
a.	Structure and Composition	6-1
	<i>IRB Structure</i>	6-1
	<i>IRB Composition</i>	6-1
b.	Appointment of IRB Members, Length of Service, and Duties	6-1
c.	Appointment IRB Chairperson, Length of Service, and Duties	6-2
d.	Alternate IRB Members	6-3
e.	Continuing Consultants to the IRB	6-4
f.	Ad Hoc Consultants	6-4
g.	Legal Counsel	6-4
h.	IRB Membership Requirements	6-4
i.	Conflicts of Interest	6-5
j.	Initial Training, Continuing Education, and Professional Development of IRB Members	6-5
k.	Evaluation of IRB Chair, Vice Chair(s), and IRB Members	6-5
l.	Telephone and Video Conferencing	6-5
7.	IRB Administrative Support	
a.	Resource Allocation	7-1
b.	Reporting Lines and Supervision	7-1
c.	Initial Training, Continuing Education, and Professional Development of IRB Staff	7-1
d.	IRB Professional Staff Duties	7-1
e.	IRB Support Staff Duties	7-2
8.	IRB Recordkeeping and Required Documentation	
a.	Record Retention	8-1
b.	Access to IRB Records	8-1
c.	IRB Records	8-1
d.	IRB Membership Rosters	8-1
e.	Education and Training Records	8-2
	<i>Research Investigator Education</i>	8-2
	<i>IRB Member and Staff Education</i>	8-2
	<i>Training Records</i>	8-2

f.	IRB Correspondence	8-2
g.	IRB Research Application (Protocol) Files	8-2
h.	IRB Database	8-4
i.	Documentation of Exemptions	8-4
	<i>Exempt Research in Educational Settings</i>	8-5
	<i>Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior</i>	8-5
	<i>Exempt Use of Existing Materials</i>	8-6
j.	Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article	8-6
k.	Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test Article	8-7
l.	Documentation of Expedited Reviews	8-6
	<i>Documentation</i>	8-7
	<i>FDA/DHHS Specified Categories</i>	8-7
	<i>Informed Consent Applies</i>	8-7
	<i>Request for Full IRB Review</i>	8-7
m.	Documentation of Convened IRB Meetings – Minutes	8-8
n.	Attendance at IRB Meetings	8-9
o.	Quorum Requirements and Voting at IRB Meetings	8-9
p.	Actions Taken by the Convened IRB	8-9
q.	Substantive Conditions (or Modifications)	8-10
r.	The Basis for Requiring Changes in or Disapproving Research	8-11
s.	Summary of Controverted Issues at Convened Meetings	8-11
t.	Required IRB Findings and Determinations	8-11

9. Procedures for IRB Review

a.	Review by the Convened IRB	9-1
b.	Initial Review by the Convened IRB	9-1
c.	Continuing Review by the Convened IRB	9-2
d.	Review of Protocol Changes by the Convened IRB.....	9-3
e.	Review of Reports of Unanticipated Problems by the Convened IRB	9-3
f.	Review of Reports of Serious or Continuing Non-Compliance by the Convened IRB	9-4
g.	Use of Primary and Secondary Reviewers with Convened IRB Reviews	9-4
h.	Expedited Review of Research	9-5
i.	Expedited Review of Minor Changes in Previously Reviewed Research.....	9-6
j.	Expedited Initial and Continuing Review: Permitted Categories	9-6
	<i>Expedited Review of Research Involving Existing Material</i>	9-7
	<i>Prospective Use of “Existing” Materials</i>	9-7

	<i>Expedited Review of Research Involving Data from Voice, Video Digital, or Image Recordings Made for Research Purposes.....</i>	9-7
	<i>Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies.....</i>	9-7
k.	Revisions to Protocols	9-8
l.	Review and Reporting of Unanticipated Problems and/or Adverse Events.....	9-8
	<i>Overview.....</i>	9-8
	<i>Adverse Event Reporting.....</i>	9-10
	<i>Reporting to Sponsor/Government.....</i>	9-14
	<i>Reporting of DSMB/DMC and Safety Reports.....</i>	9-15
	<i>Reporting of other Types of Unanticipated Problems.....</i>	9-15
	<i>Changes to Study Due to an Unanticipated Problem.....</i>	9-16
	<i>Protecting Subject Privacy In Reporting.....</i>	9-16
	<i>Continuing Review.....</i>	9-16
m.	Review of Sponsor or Cooperative Group Adverse Events of Safety Reports	9-17
n.	Review of Data and Safety Monitoring Board (DSMB) Reports	9-18
o.	Reporting and Review of Protocol Deviations/Violations	9-18
p.	Research in Emergency Situations	9-20
q.	Use of Subcommittees to Support IRB Activities	9-20
r.	Outcomes of IRB Review	9-20
	<i>IRB Review Actions</i>	9-20
s.	Expiration of Approval Period	9-21
	<i>Emergent Care</i>	9-22
	<i>Continuation of Study Activities Post Study Expiration</i>	9-23
t.	Suspension or Termination of IRB Approval	9-23
u.	Notification to Texas Health Resources Officials Regarding IRB Findings	9-24
v.	External Reporting to Regulatory Agencies Regarding IRB Findings ...	9-25

10. Criteria for IRB Approval of Research

a.	Levels of Risk	10-1
b.	Risks Minimized.....	10-1
c.	Risks Reasonable Relative to Anticipated Benefits	10-2
d.	Equitable Selection of Subjects	10-2
	<i>Inclusion of Women and Minorities</i>	10-2
	<i>Inclusion of Children</i>	10-3
e.	Informed Consent Procedures	10-3
f.	Documentation of Informed Consent	10-4
	<i>Date Stamp Required</i>	10-7

g.	Data Safety Monitoring	10-7
h.	Privacy of Subjects and Confidentiality of Data.....	10-7
i.	Additional Safeguards for Vulnerable Subjects.....	10-8
j.	Review More Often than Annually	10-8
k.	Independent Verification from Sources Other than the Investigator that No Material Changes Have Occurred Since the Previous IRB Review	10-9
l.	Consent Monitoring	10-9
m.	Advertisements and Recruitment Incentives	10-10
n.	Obtaining Consent from Non-English Speakers	10-11
o.	Payments to Research Subjects	10-12
p.	Compensation for Injury	10-12
q.	Certificates of Confidentiality	10-12
r.	Indemnity and Liability Provisions	10-13
s.	Compliance with All Applicable Laws	10-13
t.	Waiver or Alteration of Informed Consent Requirements: State or Local Public Benefit Programs	10-13
u.	Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research	10-14
v.	Waiver of Documentation of Consent	10-14
w.	Study Funding/Costs	10-15

11. Required Elements of Informed Consent

a.	Research Statement (required element #1)	11-1
b.	Reasonably Foreseeable Risks or Discomforts (required element #2)...	11-1
c.	Reasonably Expected Benefits to Subjects or Others (required element #3)	11-2
d.	Appropriate Alternatives (required element #4)	11-2
e.	Extent of Confidentiality (required element #5)	11-2
f.	Compensation or Treatment for Injury (required element #6)	11-2
g.	Contact Information (required element #7)	11-2
h.	Voluntary Participation Statement (required element #8)	11-3
i.	Additional Elements Where Appropriate	11-3
	<i>Unforeseeable Risks to Subjects, Embryos, or Fetuses</i>	11-3
	<i>Investigator-Initiated Termination of Participation</i>	11-3
	<i>Additional Costs</i>	11-3
	<i>Early Withdrawal/Procedures for Termination</i>	11-3
	<i>Significant New Findings</i>	11-4
	<i>Approximate Number of Subjects</i>	11-4
j.	Requirement for Consent by Authorized Personnel	11-4
k.	Copy to Subject	11-4
l.	Witness Signature	11-4
m.	Data Retention When Subject Withdraw.....	11-5

12. FDA-Regulated Research: Investigational Drugs, Devices, and Biologics

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

a.	FDS versus Common Rule and DHHS Requirements.....	12-1
b.	INDs and IDEs	12-1
	<i>Investigational New Drug Application (IND)</i>	12-1
	<i>Investigational Device Exemption (IDE)</i>	12-2
	<i>Biologics License Application</i>	12-2
	Application Exemptions.....	12-2
	Exemption 1.....	12-2
	Exemption 2.....	12-2
	Exemption 4.....	12-3
c.	Investigator and Sponsor Responsibilities	12-3
	<i>Basic Investigator Responsibilities</i>	12-3
	<i>Basic Sponsor Responsibilities</i>	12-4
d.	IRB Review of Medical Devices	12-4
	<i>Significant Risk (SR) Device Defined</i>	12-4
	<i>Nonsignificant Risk (NSR) Device Defined</i>	12-4
	<i>Review Procedures</i>	12-4
	<i>510(k) Devices</i>	12-5
e.	Radiology Devices and Radioactive Materials.....	12-5
f.	Adverse Events and Reporting Requirements - INDs.....	12-5
	<i>Investigators' Duty to Report</i>	12-6
	<i>Reporting Requirement</i>	12-6
g.	Adverse Events and Reporting Requirements - IDEs.....	12-6
	<i>Investigators' Duty to Report</i>	12-6
	<i>Reporting Requirement</i>	12-6
h.	Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice Versus Research	12-7
i.	Treatment INDs and IDEs	12-7
	<i>Treatment IND</i>	12-8
	<i>Single Patient Treatment IND</i>	12-8
	<i>Group C Treatment IND</i>	12-8
	<i>Orphan Drugs</i>	12-8
	<i>Parallel Track Studies</i>	12-8
	<i>Treatment IDE</i>	12-8
j.	Gene Transfer Research	12-9
k.	Emergency Use of a Test Article without IRB Review	12-9
	<i>Required Conditions</i>	12-9
	<i>Emergency Use of Drugs</i>	12-9
	<i>Emergency Use of Devices</i>	12-10
l.	Emergency Use of a Test article without Informed Consent	12-10
	<i>Required Conditions</i>	12-10
m.	Compassionate Use of Investigational Drugs and Devices	12-11
	<i>THR Requirements</i>	12-11
n.	Humanitarian Device Exemptions	12-12
o.	Planned Emergency Research	12-12
	<i>Required Conditions</i>	12-12

13. Social and Behavioral Research

a.	Social and Psychological Harms	13-1
b.	Privacy and Confidentiality Concerns	13-1
c.	Safeguarding Confidentiality	13-2
d.	Exempt Research	13-3
e.	Expedited Review of Social and Behavioral Research	13-3
f.	Research Involving Deception	13-4

14. Large Sample, Genetic, and Family History Research

a.	Research Utilizing Large Existing Data Sets	14-1
b.	Research Utilizing Data or Tissue Repositories	14-1
c.	Epidemiology Research	14-2
d.	Issues in Genetic Research	14-3
e.	Family History Research	14-3

15. Potentially Vulnerable Subject Groups

a.	Elements to Consider	15-1
b.	Pregnant Women, Human Fetuses and Neonates	15-2
	<i>Pregnant Women and Fetuses Prior to Delivery</i>	15-2
	<i>Fetuses After Delivery</i>	15-3
	<i>Placenta, Dead Fetus, or Fetal Material After Delivery</i>	15-4
	<i>Other Research Affecting Pregnant Women or Fetuses</i>	15-4
c.	Research Involving Prisoners	15-6
d.	Research Involving Children	15-7
	<i>Risk-Benefit Analysis</i>	15-8
	<i>Permitted Categories</i>	15-8
	<i>Parental Permission</i>	15-8
	<i>Assent of the Child</i>	15-8
	<i>Wards of the State and Research Setting</i>	15-8
	<i>Child Advocate</i>	15-8
	<i>Table 15-1 – Category Requirements for Permissible Research</i>	
	<i>Involving Children</i>	15-10
	<i>When Assent is Not Required</i>	15-10
	<i>Reasonable Expectation of Benefit</i>	15-11
	<i>Documentation of Assent</i>	15-11
e.	Research Involving Decisionally Impaired Subjects	15-11
f.	Research Involving Potentially Addictive Substances	15-11
g.	Research Involving Other Potentially Vulnerable Adult Subjects	15-12
h.	Fetal Tissue Transplantation Research	15-13
i.	Research Involving Deceased Persons	15-13

16. Research Misconduct: Allegations, Investigations and Reporting 16-1

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

a.	Research Misconduct	16-1
b.	Federal Funding Agency Requirements	16-1
c.	Individual Reporting Responsibility	16-1
d.	Inquiry	16-1
e.	Investigation	16-2
f.	Procedure for Allegations or Concerns Involving Research	16-2
	i. Receipt of allegation	16-2
	ii. Inquiry Process	16-21
	iii. Investigation Procedures	16-3
g.	Internal Coordination	16-4
	i. Health Hazard	16-2
	ii. Protect Assets	16-4
	iii. Protect Integrity	16-5
	iv. Protect interest of those involved	16-5
	v. Likelihood of being reported publicly	16-5
	vi. Reasonable indication of possible criminal violation	16-5
h.	Notification to External Agencies	16-5
	i. Outcome of Inquiry	16-5
	ii. Commencement of an investigation	16-5
	iii. Written request for time extension	16-6
	iv. Interim reports	16-6
	v. Early termination	16-6
	vi. Special emergency notifications	16-6
i.	Determination of Discipline	16-6
j.	Cautions and Assistance	16-7
	i. Expert Assistance	16-7
	ii. Conflicts of Interest	16-7
	iii. Anonymity	16-7
17.	Managing Conflicts of Interest	17-1
18.	How to Submit Materials to the IRB	
a.	The eIRB and Other IRB Related Forms	18-1
b.	Guidance for Investigators	
	<i>Table 18-I Guidance for Investigators: Items to Submit for IRB Review</i>	18-3
c.	IRB Deadlines for Initial Review	18-4
d.	IRB Deadlines for Continuing Review	18-4
e.	Communication of Determinations	18-4
	<i>Table 18-II Notice of Adverse Events and Unanticipated Problems....</i>	18-5
	<i>Table 18-IV Risk Determination for Continuing Review.....</i>	18-8
	<i>Table 18-V The THR IRB Review Process</i>	18-10

Texas Health Resources
Corporate Policy for Protection of Human Research Subjects

Chapter 1. The Ethical Mandate to Protect Human Subjects

Human subject research at Texas Health Resources (THR) Institutions must be carried out in conformity with the basic ethical principles governing research involving human subjects. The following events are important milestones in the development of protections for human subjects in research. (Complete documents are provided via the [THR IRB website](http://www.texashealth.org/irb) (www.texashealth.org/irb). All researchers and staff should have access to this website.)

- a. The Nuremberg Code.** The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related research experiments. The Nuremberg Military Tribunal developed ten principles, known as *The Nuremberg Code*, to judge the Nazi doctors. The significance of the Code is that it addressed the necessity to require the voluntary consent of the human subject and that any individual “who initiates, directs, or engages in the experiment” must bear personal responsibility for the quality of consent.
- b. The Declaration of Helsinki.** Similar principles have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects* (1964, revised 1975, 1983, 1989, 1996, 2000, which calls for prior approval and ongoing monitoring of research by independent ethical review committees).
- c. The Belmont Report.** Revelations about the 40-year United States Public Health Service Syphilis Study at Tuskegee and other ethically questionable research resulted in legislation in 1974, calling for regulations to protect human subjects and for a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to examine ethical issues related to human subject research.

The Commission’s final and most influential report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, defines the ethical principles and guidelines for the protection of human subjects. Perhaps the most important contribution of *The Belmont Report* is its elucidation of three basic ethical principles:

- (i) Respect for Persons (operationalized by obtaining informed consent);
- (ii) Beneficence (operationalized by weighing risks and benefits); and
- (iii) Justice (operationalized by the fair selection of subjects).

The Belmont Report also provides important guidance regarding the boundaries between Biomedical Research and the practice of medicine.

THR Entities are guided by the ethical principles concerning human involvement in research that are set forth in the Belmont Report. All IRB members and all IRB professional and support staff should be thoroughly familiar with these most basic ethical principles.

Chapter 2. The Regulatory Mandate to Protect Human Subjects

Federal regulations require specific protections for human subjects. (These and other regulatory documents are provided via the [THR IRB website](#). All researchers and staff should have access to this website.)

- a. Department of Health and Human Services (DHHS) Regulations.** DHHS regulations at [45 CFR Part 46 Subpart A](#) constitutes the Federal Policy (Common Rule) for the protection of human subjects. This Common Rule applies to any human subject research supported by any of the seventeen agencies of the Federal government that support human subject research.

The DHHS human subject regulations also include additional protections for pregnant women, human fetuses and neonates ([Subpart B](#)); prisoners ([Subpart C](#)); and children ([Subpart D](#)). These regulations are enforced by the DHHS Office for Human Research Protections (OHRP).

As a matter of policy, THR meets the requirements set forth in [45 CFR Part 46](#), for all DHHS-supported research, and, except for the requirements for reporting information to DHHS, all other research without regard to source of funding.

- b. Food and Drug Administration (FDA) Regulations.** FDA has codified informed consent ([21 CFR Part 50](#)), IRB ([21 CFR Part 56](#)), and child protection (61 FR 20589 and [21 CFR Part 50, Subpart D](#)) regulations that are almost identical to the DHHS regulations. Additional FDA regulations relevant to the protection of human subjects address Investigational New Drug Applications ([21 CFR Part 312](#)), Biological Products ([21 CFR Part 600](#)), and Investigational Device Exemptions ([21 CFR Part 812](#)).

In general, FDA human subject regulations apply to clinical investigations and other research involving products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

IRB review and approval is required for all clinical investigations and all other research involving products regulated by FDA for human use, even where an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is not required.

- c. The Assurance and IRB Registration Process.** THR maintains a Federalwide Assurance (FWA) of Protection for Human Subjects approved by the DHHS Office for Human Research Protections (OHRP). The FWA authorizes THR to conduct human subject research that is supported by DHHS or any of the other Federal “Common Rule” agencies.

The FWA covers all human subject research conducted (i) by any THR employee or agent or in which THR is engaged; or (ii) in any THR wholly owned or controlled Entity (THR Entities). Thus, any Investigator who (i) acts as an employee or agent of any THR Entity, or (ii) conducts research within any THR facility or with THR equipment or resources is bound by THR’s human subject protection policies and requirements.

THR Agent Defined. For the purposes of this policy, a THR agent is any individual who (i) acts on behalf of THR or any THR Entity, or (ii) represents herself/himself as affiliated with THR or any THR Entity in (a) the planning, design, conduct (including data analysis), or support of research; (b) the solicitation of funds or in-kind support for research; (c) the recruitment of research subjects; (d) obtaining the informed consent of research subjects; or (e) the publication or presentation of research results.

Coverage Under the THR FWA. All THR Entities are covered under the THR FWA and are authorized to cite the FWA Number in communicating with Federal agencies. As a matter of corporate policy, no individual THR Entity may hold an OHRP Assurance apart from or in addition to the THR FWA.

Operation of THR IRB. THR operates an Institutional Review Board (IRB) as necessary to accommodate the volume of human subject research taking place within its facilities. The IRB is constituted and administered with the concurrence of the THR Institutional Official for Human Subject Protection. In addition, the IRB must participate in the THR Research Compliance and Education Program under the oversight of the THR Institutional Official.

- d. THR Policies.** As indicated above, THR meets the requirements of the DHHS human subject regulations for all of its research, without regard to source of funding. THR also complies with the requirements of FDA regulations where applicable. THR policies and procedures for implementing the requirements for protecting human subjects are provided in the subsequent Chapters of this manual. THR Entities may have additional Entity and/or departmental policies and procedures that further describe

Texas Health Resources
Corporate Policy for Protection of Human Research Subjects

processes, controls and other information as to “how” the facility carries out research activities. Any such policies and/or procedures must be consistent with the standards set forth in this manual.

Chapter 3. Types of Human Subject Research

All research involving human subjects conducted at THR Entities must be reviewed by the THR Institutional Review Board (IRB).

a. Definition of Human Subject and Research.

Research Defined. Federal regulations ([45 CFR 46.102\(d\)](#)) define research as “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”

Systematic Investigation Defined. The systematic gathering and analysis of information.

Generalizable Knowledge Defined. Knowledge that could be applied to populations outside of the patients served by the covered entity (i.e., THR hospital(s) or wholly owned entity(s)).

Research or Clinical Investigation Defined. Any experiment that involves a test article and one or more human subjects that is subject to Food and Drug Administration (FDA) requirements for research or marketing permits [21 CFR Part 50.3(c) and 56.102(c)].

Human Subject Defined. An individual who is the object of study in a research project. Under the Federal Policy (Common Rule), human subject means a living individual about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information [45 CFR 46.102(f)]. Under FDA regulations, “human subject” means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient [21 CFR 50.3(g) and 56.102(e)]. An individual on whose specimen a device is used. For medical devices studies involving in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects.

Private Information Defined. Private information includes information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded.

Identifiable Defined. Identifiable means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

- b. **Level of Risk Defined.** Human subject research governed by Federal regulations falls into one of two categories: minimal risk or greater than minimal risk.

Minimal Risk Defined. 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 ([45 CFR 46.102\(i\)](#); [21 CFR 56.102\(i\)](#)).

Minimal Risk for Prisoners. In the case of research involving prisoners, 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.

- c. **Types of Human Subject Research.** The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research.

Biomedical Research. Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of Biomedical Research.

Social and Behavioral Research. The goal of Social and Behavioral Research is similar to that of Biomedical Research—to establish a body of knowledge and to evaluate interventions—but the content and procedures often differ. Social and Behavioral Research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention. See [Chapter 13](#) for additional discussion.

Clinical Research. Clinical research involves the evaluation of biomedical or behavioral interventions related to disease processes

or normal physiological functioning. See [Chapter 12](#) for additional discussion.

Epidemiology Research. Epidemiology research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, interventions, or delivery of services to affected populations. Some epidemiology research is conducted through surveillance, monitoring, and reporting programs—such as those employed by the Centers for Disease Control and Prevention (CDC)—whereas other epidemiology research may employ retrospective review of medical, public health, and/or other records. Because epidemiology research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may qualify for exemption or expedited review. In all cases, the IRB, not the individual investigator, will determine when IRB review of the activity is required. See [Chapter 14](#) for additional discussion.

Repository Research. Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB should review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols. See [Chapter 14](#) for additional discussion.

Pilot Studies. Pilot studies involving human subjects are considered human subject research and require IRB review.

- d. Quality Improvement (QI) Activities as Human Subject Research.** Quality Improvement activities attempt to measure the effectiveness in order to improve programs or services.

Quality Improvement activities constitute human subject research, and require IRB review, when they are designed or intended, at least in part, to develop or contribute to generalizable knowledge.

Alternatively, Quality Improvement activities that are designed solely for internal program evaluation or improvement purposes, with no external application or generalization intended, these activities do

not constitute human subject research, and usually do not require IRB review.

For example, suppose a medical department at a THR Entity conducts a review of patient records and then contacts patients to identify cases where recommended follow-up did not occur. If the sole intent is to improve the rate of follow-up at the THR facility where the review occurred and/or at other THR entities, then the activity is not human subject research and does not require IRB review.

However, if the intent of the activity, at least in part, includes extending the findings to patients at facilities outside THR, or disseminating the findings in such a way that applicability outside THR is stated or implied, then the activity does constitute human subject research, and does require IRB review. If the material (data) to be analyzed and presented outside of the local setting includes identifiable private information – information linked to one or more persons (for example, patients whose data were included in the QI initiative) – then the research would involve a human subject (45 CFR 46.102(f)) and a THR IRB protocol must be submitted and approved before analysis and presentation. If the material (data) were anonymized and de-identified before analysis and presentation, the IRB Office could declare the activity not to be subject to IRB review because the project would not involve a human subject (45 CFR 46.102(f)) and not be subject to the research provisions of the Privacy Rule (HIPAA), (45 CFR 164.500(a)) or FDA regulations (21 CFR 56.102(c)).

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal THR purposes lead to a desire to generalize and disseminate the results for application outside THR), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

Where any disagreement arises about whether a Quality Improvement activity constitutes human subject research, the IRB, not the individual investigator, will determine when IRB review of such activities is required.

- e. Research Activities versus Commercial Services.** THR facilities and laboratories sometimes provide tests or other services to researchers solely on a commercial basis (e.g., an appropriately

qualified THR laboratory performs analyses of blood samples for investigators solely on a commercial basis).

Provision of such services solely on a commercial basis does not constitute THR human subject research and does not require THR IRB review, provided that all of the following conditions are met:

- (i) The research is not otherwise conducted at THR;
- (ii) The research does not otherwise involve THR employees or agents (e.g., as co- or sub- investigators, as study coordinators, in planning or analysis, or receiving publication credit) or in which THR is defined as engaged;
- (iii) The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges; and
- (iv) The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality.

However, if THR personnel are involved in any way that is more than merely providing a commercial service, then prospective review and approval of THR IRB is required.

- f. Engagement Defined.** THR is engaged in the research study when: a) an Entity of Texas Health Resources has contracted with a sponsor to conduct a clinical trial; or b) Texas Health Resources' employees or agents provide administrative support, research coordination or hospital services to investigators in the conduct of a clinical trial; or c) an investigator recruits for the research study using THR premises or communication resources including study subject recruitment or other study solicitation activities.

For a study to be reviewed by the THR IRB, the principal investigator or a co-investigator must be an employee, medical staff member or otherwise be affiliated with a THR Entity and have expertise and/or a "scope of practice" that is consistent with the needs of the study.

Chapter 4. Shared Responsibilities for Protecting Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust among the Institution, Investigators and their research staff, the subjects who enroll in research, and the IRB. A clear delineation of the responsibilities of each of these parties can help protect the participants who volunteer for research.

- a. THR Institutional Responsibilities.** It is the responsibility of THR to assure Federal Agencies in writing that it will comply with regulations governing the protection of human subjects. As part of its written Assurance to the government, THR must develop policies and procedures for conducting human subject research in a responsible and ethical fashion, including how research will be reviewed by the IRB, the reporting of unanticipated problems to the IRB and appropriate regulatory bodies, and other issues.

THR Board of Trustees. The THR Board of Trustees has ultimate authority for the oversight and monitoring of this Corporate Policy for the Protection of Human Subjects. The Board may designate a Board Committee for this purpose.

THR Institutional Official. The THR Board of Trustees shall designate a THR officer to serve as the THR Institutional Official for research activities. The THR officer, so designated, serves as the Institutional Official for Human Subject Protection under THR's Assurance and is ultimately responsible for overseeing the protection of human subjects within THR. These responsibilities include:

- Developing THR policies governing the IRB, all THR human subject research, and all THR investigators and research personnel;
- Maintaining open channels of communication between the THR IRB, research investigators and staff, and administration;
- Working with the THR IRB to see that the IRB is provided with sufficient meeting space and staff to support its substantial review and record keeping responsibilities;
- Monitoring the operation and administration of the IRB and determining that they function in accordance with the assurances provided in compliance with all Federal, State, and local laws and regulations that govern human subject protection in the conduct of research;

- Notifying the THR Legal Counsel and the THR Chief Compliance Officer regarding (i) any unanticipated problem involving risks to subjects or others; (ii) any serious or continuing non-compliance with IRB requirements by research investigators; or (iii) any for-cause suspension or termination of IRB approval;
- Notifying OHRP and FDA of such incidents in accordance with applicable Federal regulations. Such notice will be accomplished in coordination with THR Legal Counsel, the THR Chief Compliance Officer; and
- Implementing a research compliance monitoring process and providing compliance monitoring reports, as appropriate, to (i) the THR Chief Compliance Officer; (ii) THR Legal Counsel; (iii) senior THR management officials; (iv) the THR Board of Trustees; (v) THR IRB; (vi) senior management officials of relevant THR Entities; and (vii) THR Entity Boards of Trustees, as applicable.

The THR Institutional Official, the THR Chief Compliance Officer, and the THR Legal Counsel have direct access to any member of senior management including the THR Chief Executive Officer and/or THR Board of Trustees, if needed, to fulfill THR compliance monitoring and reporting responsibilities.

- b. The Institutional Review Board (IRB).** An IRB is an appropriately constituted group that has been formally designated by each Entity Board to review and monitor research involving human subjects. In accordance with the Common Rule, DHHS regulations, and FDA regulations, the IRB has responsibility for approving, requiring modification in (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and initial and continuing review procedures.
- c. The Principal Investigator.** As the individual responsible for the implementation of research, the Principal Investigator bears direct responsibility for protecting every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits. In addition, the Principal Investigator and all members of the research team must comply with the findings, determinations, and requirements of the IRB. The Principal Investigator must also be responsible for the adequacy of both the informed consent document and the informed

consent process, regardless of which members of the research team actually obtain and document consent.

Who May Serve as Principal Investigator at THR? The Principal Investigator must be a THR employee, a THPG employee/physician or a non-employee or physician appropriately credentialed at THR.

Principal Investigators' Responsibilities. **Principal Investigators must ensure:**

- (i) That all human subject research which they conduct at THR Entities or as employees or agents of THR or in which THR is engaged has received prospective review and approval by the THR IRB;
- (ii) That continuing review and approval of the research has been secured in a timely fashion by the THR IRB;
- (iii) That the research is conducted at all times in compliance with all applicable Federal, State, and local regulatory requirements and with the determinations of the THR IRB; and
- (iv) That the investigator has reviewed THR's approved Assurance of Compliance with DHHS Regulations for Protection of Human Research Subjects, relevant FDA regulations, and the Belmont Report.

Notice of Audit/Inspection From Regulatory Authorities. Upon initial notification from regulatory authorities (e.g., FDA, OHRP, etc.) of an impending audit/inspection, the PI or designee must notify the Research Compliance Officer. The notification must be reported prior to the end of the next working day from date of notification by the regulatory authority(s). Any subsequent updates and/or developments (i.e., observations, findings, reports, correspondence, etc.) must be reported to the Research Compliance Officer prior to the end of the next working days of receipt or first knowledge by the PI or designee.

Changes to Approved Research. No changes in approved research may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period.

Protocol violations that may affect subject rights, subject safety or welfare, the integrity of the research study and/or the subject's willingness to continue study participation must be reported to the IRB within **10 working days** of the Principal Investigator becoming aware of the violation. Any emergent change from the IRB-approved

application made without prior IRB review must be reported within **5 working days** of its occurrence. (See also Chapter 9 for detailed reporting information.)

Adverse Events/Notice of Unanticipated Problems. One of the charges of the IRB is to review “any unanticipated problems involving risks to subjects or others” (45 CFR 46.103(b)(5)(i) & 21 CFR 56.108(b)(1)).

An unanticipated problem involving risks to subjects or others (UP) is any unanticipated incident, event, or problem that is related to the conduct of the research and poses a risk to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research). Investigators, IRB staff, and IRB members are advised to fulfill their functions described in this chapter based on this definition of an UP.

In accordance with Federal regulations, THR investigators are required to report UPs to the IRB.

UPs may occur at non-THR sites, but could be relevant to the protection of research subjects at THR, and these UPs should also be reported to the THR IRB for review. If investigators are unsure as to whether a particular incident or problem represents an UP, they are expected to contact the Office of Research Compliance for guidance or to submit a report to the IRB for consideration.

Adverse Events (AEs) are a category of unanticipated problems. Accordingly, the THR IRB requires that investigators report internal (local) AEs that may affect the welfare of participating subjects.

As a general rule, AEs that are:

- serious,
- unexpected and are
- related, probably related or possibly related to the study intervention(s)

must be reported **within 10 working days** after the investigator becomes aware of the event whether the AE occurs at THR or at another study site.

Notice of Completion, Discontinuance of Project or Withdrawal of Exemption. To allow for substantive and meaningful review of research activities at the close of a study, within three months after the completion or discontinuance of a research project, or of withdrawal of the exemption for a research project, the investigator

must notify the IRB and the sponsor and make an accurate and adequate final report to the IRB and the sponsor. Refer to Table 17-II for investigator reporting requirements.

Continuing review and re-approval of research is required at least annually as the project continues to involve human subjects. A research project continues to involve human subjects as long as the investigators continue to obtain data about the subjects of the research through intervention or interaction with them or identifiable private information (including identifiable biological specimens originating from living individuals) about the subjects of the research.

- Collecting or receiving identifiable private information from any source that is not already in possession of the investigator;
- Collecting identifiable private information by observing or recording private behavior without interacting or intervening with the human subjects;
- Using, studying, or analyzing identifiable private information even if the information was already in the possession of the investigator before the research begins.

A research project no longer involves human subjects once the investigators have finished obtaining data through the interaction or intervention with subjects or obtaining identifiable private information about the subjects, including using, studying, or analyzing identifiable private information. Once these research activities are completed a study may be closed.

Note that a study may be closed when the only remaining activity involves the analysis of aggregate data sets without individual subject identifiers. Additionally, if an investigator is simply maintaining individually identifiable private information without using, studying, or analyzing such information this does not constitute human subjects research and therefore does not require continuing review. The study may be closed.

Study closures will be reviewed, processed, and acknowledged by IRB staff.

Studies closed to further accrual/enrollment, but planning to continue with subject follow-up or data analysis, are required to maintain current IRB approval.

If terminating employment or other association with THR, the investigator must either (i) close the study at THR and submit a closure form via the eIRB submission system (eIRB is defined as any form of electronic IRB submission system) or (ii) transfer the protocol to another THR investigator via an eIRB amendment form).

For industry sponsored research, the investigator should always consult and obtain documentation from the sponsor that the study can be closed at the THR site prior to notifying the THR IRB of the study closure.

For multi-center studies, continuing review of the research by the THR IRB is no longer required after all human subject research activities have been completed at THR, even if (i) interactions or interventions with subjects may be occurring at other study sites; or (ii) data analysis of identifiable private information is ongoing at another central site that collects and analyzes data from all study sites. If a THR investigator is the central site for a multi-site study, then the investigator should not close the THR study until all (i) interactions or interventions with subjects occurring at other study sites; or (ii) data analysis of identifiable private information (including HIPAA protected health information) is completed at all other study sites.

If applicable, the investigator shall report any findings from a closed study when those affect the safety and medical care of past subjects. Findings will be reported for two years after the closure of the study.

Subsequent Use of Data From Closed Research. Subsequent use of data from closed research for another research purpose, whether by the original investigator or other investigators, may constitute human subjects research requiring IRB approval or certification of exemption from IRB review. Please consult the IRB office prior to use of data.

Investigator Records. Investigators must maintain research records for an amount of time that is consistent with the Record Retention – Human Subject Research table (Table 18-III – See separate table located on the IRB website/policy page and THR PolicyConnect), whether or not the research is Federally funded. Additional requirements for research retention vary with the type of research conducted and provisions of the investigator's funding source. The investigators should comply with the THR and sponsor record retention requirements, whichever is longer.

Such records must be made available for inspection and copying to the IRB Members, THR Institutional Official, the THR Chief Compliance Officer, THR Legal Counsel and/or department or agency supporting or conducting the research at reasonable times and in a reasonable manner immediately upon request.

Protocols that are conducted under FDA regulations must, at a minimum, retain research records in accordance with [21 CFR 312.57](#), [21 CFR 312.62](#) and/or [21 CFR 812.140](#).

Except as required by law or released with the written permission of the subject, investigators are required to maintain appropriate safeguards (i.e., research records filed in a locked cabinet only accessible to authorized study personnel) to ensure the privacy and confidentiality of subject records.

At a minimum, signed Privacy Rule Authorizations must be retained for six years [§164.530(j)(1)(ii)].

If a covered entity has used or disclosed protected health information (PHI) for research with an IRB or Privacy Board approval of waiver or alteration of Authorization, documentation of that approval must be retained by the covered entity, at a minimum, for 6 years from the date of its creation or the date it was last in effect, whichever is later.

Refer to the THR Corporate Policy for Privacy under HIPAA for additional privacy and research information.

Hospital Affiliation. If the research study is not approved by the THR IRB, the investigator may not use a THR hospital affiliation in any portion of the research or publications related to it.

- d. Other Members of the Research Team.** Every member of the research team is responsible for protecting human subjects. Co or sub-investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures; adhere rigorously to all protocol requirements; inform investigators of all applicable adverse subject reactions or unanticipated problems; oversee the adequacy of the informed consent process; and take whatever measures are necessary to protect the safety and welfare of subjects.

Researchers at every level are responsible for notifying the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the IRB of which they become aware, whether or not they themselves are involved in the

research. Researchers may also notify the THR Institutional Official, THR Chief Compliance Officer, or THR Legal Counsel directly of any compliance concerns they may have.

- e. **Research Subjects.** Subjects may be viewed as having certain responsibilities as well. They can be expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation in good faith. While participating, they should also make every reasonable effort to comply with protocol requirements and inform the investigators of unanticipated problems.

Subjects' Right to Withdraw. Subjects always have the right to withdraw from their participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.

Chapter 5. Institutional Review Board (IRB) Roles and Authorities

An Institutional Review Board (IRB) is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the Common Rule, DHHS regulations, and FDA regulations, the IRB has responsibility for approving, requiring modification in (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

- a. Human Subject Protections under Federal Regulations.** Federal regulations at [45 CFR Part 46](#) require that Institutions engaging in human subject research supported by the Department of Health and Human Services (DHHS) devise mechanisms for the protection of human subjects. The regulations require that each Institution conducting human subject research file a written “Assurance” of protection for human subjects and designate one or more Institutional Review Boards (IRB) to review its human subject research. (These and other applicable regulations are provided via the [THR IRB website](#) . All researchers and staff should have access to this website.)

THR Federal-wide Assurance and Registration of THR IRB. The filing of the THR Assurance and the registration of the IRB is the responsibility of the designated THR Institutional Official for Human Subject Protection.

The IRB operates under the THR Federalwide Assurance approved by the DHHS Office for Human Research Protections (OHRP).

- b. Corporate Authority and Oversight of THR IRB.** The THR Institutional Official is ultimately responsible for oversight of regulatory compliance for all research activities conducted under the auspices of THR. Such oversight will be accomplished in coordination with, and with input from, the THR Chief Compliance Officer, and in consultation with THR Legal Counsel.
 - **IRB Review Fees.** THR IRB fees for prospective/initial review and for continuing review will be reviewed periodically Research Activities Compliance Committee (RACC) to determine if the fee is market-based and adequate when considering the time and resources consumed in performing such reviews and make a recommendation to the responsible

system executive. Refer to the IRB Fee webpage on the THR IRB website for actual fee amounts and processing procedures.

IRB fees are due prior to final IRB approval.

The following are exempt from IRB submissions fees:

- NIH Funded study
- NIH-like funded study, if overhead is included and is designated for distribution to THR to cover IRB fee.
- Unfunded studies of THR employees in a degree program (i.e. nursing students, medical students, residents)
- Studies that are requested by and which solely benefit a THR hospital (Hospital Initiated study)
- Unfunded Data/Record review study in which there is no financial benefit to the Physician Investigator
- Unfunded investigator-initiated study, with approval by THR legal counsel.
- Amendments requested by the IRB and administrative changes to study staff.

Any request for fee exemption not addressed above must be approved by the Institutional Official or designee.

- c. Purpose of the IRB.** An IRB's primary responsibility is to protect the rights and welfare of participants involved in human subject research. In doing so, the IRB monitors human subject research to determine that it is conducted ethically, and in compliance with the Federal regulations, the requirements of applicable State law, THR's Assurance, and THR's policies and procedures for protecting human subjects.

The IRB fulfills these responsibilities by conducting prospective and continuing review of human subject research, including review of the protocol and grant applications or proposals (for Federally-supported research), the informed consent process, procedures used to enroll subjects, and any reportable adverse events or unanticipated problems reported to the IRB (refer to Chapter 9 for specific information). Prospective review and approval of research or changes to previously approved research ensures that research is not initiated without IRB review and approval.

In their communications to investigators, the IRB will make investigators aware of the requirement to submit protocol changes to

the IRB for review and approval before initiation of such changes except where necessary to eliminate apparent immediate hazards to the subject (refer to Chapter 9 for specific information).

d. Scope of the IRB's Authority.

Approval of THR Entity Where Research Will Be Conducted. The THR Entity where the research will be conducted must provide review and approval prior to submission of a protocol application to the IRB. In the event that a protocol is submitted to the IRB prior to the Entity's review and approval, the IRB may review and approve the protocol contingent upon receiving approval from the THR Entity where the research will be conducted.

Requirement for Prospective Review and Approval. All human subject research conducted at any THR Entity or by any of THR's employees or agents or in which THR is engaged must be prospectively reviewed and approved by the THR IRB. No human subject research may be initiated or continued at any THR Entity or by any of THR's employees or agents or in which THR is engaged without prospective approval of a THR IRB. If a continuation is not submitted and given final approval by its expiration date the study's IRB approval will expire. After expiration, all research activities must stop, including any research related interventions, recruitment, data collection, data sharing/reporting and analysis of identifiable data, and no new subjects may be enrolled (refer to Chapter 9 for additional information).

Adding a New Site to an Existing Approved Protocol. Any THR Entity or investigator desiring to add a new THR site to an existing THR IRB-approved protocol must submit the request with all required materials to the THR IRB.

Independent Conduct of the Same Research at Two THR Sites. If an independent protocol is required as described above, or if a THR investigator wishes to conduct a protocol independent of its conduct at another THR site, a separate protocol and a convened review (assuming the protocol does not qualify for expedited review) are required for implementation of the protocol at the second site.

Power to Take Action. Any IRB designated by the THR Institutional Official is empowered to take any action necessary to protect the rights and welfare of human subjects participating in THR research. The IRB has the authority to approve, require modifications in, or disapprove the respective Institution's human subject research.

Power to Suspend or Terminate Enrollment. The IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects in the respective research as it determines necessary for the protection of those subjects, especially in instances of serious or continuing noncompliance. The IRB has the authority to observe and/or monitor the respective Institution's human subject research to whatever extent it considers necessary to protect human subjects and assure compliance with applicable laws and regulations.

Cases of Serious or Continuing Noncompliance. In cases of serious or continuing noncompliance, the IRB may: (i) disqualify an investigator from conducting a particular research project or research altogether at the Institution; (ii) require education and training in the ethics and regulations of human subject research; or (iii) any other reasonable measure deemed appropriate to protect the rights and welfare of research subjects.

Withdrawal of Pending Studies. Studies that remain in a state of pre-submission (study created in the eIRB but not formally submitted to the IRB for review) for 180 days (approximately 6 months) will be automatically withdrawn from the electronic system. The Principal Investigator will have to request the withdrawal be revoked if they choose to continue the study.

e. Appeal of IRB Determinations.

No Set Aside or Overrule Permitted. No committee or official at THR may set aside or overrule a determination by the THR IRB to disapprove or require modifications in THR's human subject research.

Notice to Investigator. The IRB must provide the research investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the investigator an opportunity to respond in person or in writing within 90 days or the study will be closed. If a study is closed a new application will be required to be submitted.

Investigator Response and Appeal. THR IRB must carefully and fairly evaluate the investigator's response in reaching its final determination. There is no limit to the number of times a research project can be revised and re-submitted to the IRB for consideration.

f. Other THR IRB Responsibilities. As part of its obligation to report its findings and actions to the organization, the IRB will regularly

forward copies of its meeting minutes, which will include information on IRB findings and actions, to the THR Institutional Official.

- (i) Any IRB member may bring any matter directly to the attention of the THR Institutional Official, the THR Chief Compliance Officer, or THR Legal Counsel when warranted.
- (ii) The THR Institutional Official may establish additional reporting or communication relationships between the IRB and other officials or other committees (including the THR Board or Board committee) as deemed appropriate.
- (iii) The IRB may require that proposed research be reviewed and approved by an appropriately designated Committee, as deemed appropriate.
- (iv) The IRB must report any serious and unanticipated problem involving risks to subjects or others to the THR Institutional Official, THR Legal Counsel, and/or the THR Chief Compliance Officer.
- (v) All persons conducting research within any THR Entity, and all persons acting as employees or agents of THR regardless of location, must comply with all requirements of the IRB in the conduct of human subject research.
- (vi) All persons conducting research within any THR Entity, and all persons acting as employees or agents of THR regardless of location, must provide the THR Institutional Official and the IRB with copies of any reports, audit findings, or correspondence to or from any regulatory agency (such as OHRP or FDA) that bear upon the protection of human subjects in research in which they are involved **within 10 working days**. The THR Institutional Official is responsible for coordination with THR Legal Counsel and the THR Chief Compliance Officer, as appropriate. Refer to the Table 17-II for investigator reporting requirements.

g. Responsibilities to Regulatory Agencies. The IRB must comply with the requirements of all relevant regulatory agencies including [the DHHS Office for Human Research Protections \(OHRP\)](#) and the [Food and Drug Administration \(FDA\)](#). Copies of any reports or correspondence to or from such agencies must be provided by the IRB to the THR Institutional Official, who will (in consultation with THR Legal Counsel) determine whether any additional notifications are necessary.

h. THR IRB Review of Non-THR Research. Research that is not conducted either (i) by a THR employee or agent, or (ii) at a THR Entity or (iii) THR is not considered engaged is not considered THR research. The IRB will not accept responsibility for review and oversight of such non-THR research without the written agreement

of the THR Official, and in accordance with applicable regulatory requirements. Any such arrangement must also be accompanied by a written agreement specifying the responsibilities of the non-THR investigator and/or non-THR Institution, and of THR and its IRB.

- i. Relationship of the IRB to Other Institutions.** The IRB operated by THR may be designated for review of research under another Institution's (non-wholly owned or controlled by THR) Assurance only with the written agreement of the THR Institutional Official and in accordance with applicable regulatory requirements. Any such designation must be accompanied by a written agreement specifying the responsibilities of THR and its IRB under the other Institution's Assurance, if applicable. The IRB operated by THR has no authority over, or responsibility for, research conducted at other Institutions in the absence of such a written agreement.
- j. Human Subject Protection Education Program.** THR is required under its OHRP-approved FWA to have a plan to provide education about human subject protections for research investigators and IRB members and staff. The THR Institutional Official is responsible for developing and implementing an education plan, and shall determine the education requirements needed for THR personnel to participate in the conduct of human subject research and for IRB members and staff to be seated.
- k. Relationship of the IRB to IND/IDE Sponsors.** Unless specifically required by an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) sponsor or by the IRB, no written notifications of IRB decisions will be provided to IND/IDE Sponsors by the IRB. The Principal Investigator serves as the communications link between the IRB and the Sponsor for this purpose. For FDA regulated test articles, such linkage is agreed to by the Sponsor and Principal Investigators when they sign the [FDA Form 1572](#), Statement of Investigator or the investigator's agreement (for device studies).
- l. Compliance Review and Oversight of Human Protection Activities.** The THR Institutional Official (in coordination with the THR Chief Compliance Officer and THR legal counsel) is responsible for compliance oversight and review of THR's systemic protections for human subjects. This oversight and review may involve auditing of IRB files, subject records, investigator research files, or regulatory materials maintained by investigators and their staff. The review and oversight responsibilities for human subject research activities include, but are not limited to, the following:

- (i) Conducting compliance monitoring and auditing site visits to periodically review IRB and PI documentation and determine compliance level with assurances, OHRP and FDA requirements;
 - (ii) Preparing reports to the IRB, the THR Chief Compliance Officer, THR Legal Counsel, and the THR Board or Board designated committee based upon site visit findings. If warranted, the THR Institutional Official and/or the Chief Compliance Officer has the authority to require corrective action or to forward any matter to the THR Board or Board designated Committee if appropriate corrective action is not taken promptly to address any confirmed compliance deficiencies;
 - (iii) Reviewing THR policies, the Corporate Policy for Protection of Human Research Subjects and educational materials periodically to determine if they are maintained and updated appropriately; and
 - (iv) Participating in regulatory inquiries and/or correspondence with regulatory authorities concerning protection of human research subjects.
- m. Privacy Board Functions and Determinations.** The IRB operated by THR shall serve as the Privacy Board as required by HIPAA, [45 CFR 164.501](#), [164.508](#), [164.512\(i\)](#). Functions include review and determinations of requests for Waiver or Alteration of Authorization to use or disclose Protected Health Information in Research. Refer to the THR Corporate Policy on Research Privacy for the full discussion of this function and process. The Policy can be accessed via the [THR IRB website](#) . All researchers and staff should have access to this website.
- n. Reliance on the IRB of Another Institution, Organization, or an Independent (Commercial) IRB.**

Research Eligible for Reliance on an External IRB

THR will consider relying on an external qualifying commercial IRB for studies that meet **all** of the following criteria:

- Phase III, or IV Research; and
- Sponsor-initiated (defined as Sponsor created, designed, and developed); and
- Sponsor-funded; and
- Multi-site; and
- Main study already possesses external IRB approval

THR will consider relying on a qualifying external IRB review for the following study types:

- A federally funded or cooperative group study utilizing review by another IRB that is deemed to be appropriate per the Institutional Official or designee;
- Certain types of registry studies deemed eligible per the Institutional Official or designee;
- Special programs of research conducted at THR deemed eligible per the Institutional Official or designee;
- Other special circumstances not described above deemed eligible per the Institutional Office or designee.

Research Not Eligible for Reliance on an External IRB

The following types of studies require the use of the THR IRB except as determined by the Institutional Official or designee:

- Phase I and II Research;
- Studies that involve the collection of genetic specimens and information that is not collected as part of the patient's standard of care treatment;
- Research involving the storage of genetic specimens;
- Expanded Access/Compassionate Use Requests;
- If the use of an external IRB has been authorized the following will apply:
 - Approval by the external IRB only extends to the initial study and does not constitute any future use of genetic specimen information;
 - Specimens may not be provided to the Sponsor.

Criteria for Selecting a Qualifying External IRB

The Institutional Official or designee has the final authority to determine if the IRB is appropriately qualified for a reliance agreement. The criteria that will be used in evaluating the external IRB includes but is not limited to the following:

- The external IRB is currently registered with OHRP and the FDA
- The external IRB is in good standing with the federal regulatory agencies (i.e. no recent warning letters or investigations)
- For commercial IRBs, the IRB should be accredited by AAHRPP
- For non-commercial IRBs the preference is that the IRB be accredited by AAHRPP. The Institutional Official or designee may authorize reliance on a non-accredited IRB if the IRB is determined to meet THR standards.
- The IRB must be located within the United States
- Institutional Officials determination for ongoing monitoring may affect the decision

- Such other factors the Institutional Official may deem appropriate.

IRB Reliance Agreement

In accordance with OHRP guidance, when THR relies on an external IRB for review and approval of human subjects research the relationship will be documented with an appropriate IRB reliance agreement. The reliance agreement may cover a single study, multiple studies, or a program of research.

Conflict of Interest Review for Studies Relying on an External IRB

Studies submitted to an external IRB must meet the THR Corporate Policy on Conflicts of Interest Involving Human Subject Research (COI policy).

THR requires completed and signed COI forms for all study personnel listed on studies requesting reliance on an external IRB. The forms are reviewed by IRB staff before authorization to rely on an external IRB will be released. If a COI is reported that triggers the provision of the policy, the COI will be reviewed by the THR COI Committee in accordance with the COI policy. The THR COI committee will determine the COI management plan that must be presented to the external IRB prior to final approval.

Once a study is approved by the external IRB, any changes to existing COIs or any new COIs that are identified during the course of the study must be reported to the THR IRB Office.

Chapter 6. IRB Structure and Membership

a. Structure and Composition.

IRB Structure. The IRB is structured as a committee of THR under the THR Federalwide Assurance (FWA). IRB committee members are appointed by the designated THR Institutional Official.

IRB Composition. In accordance with DHHS and FDA regulations, the IRB is comprised of persons from various disciplines and departments, including non-scientific members, and community representatives not otherwise affiliated with THR. IRB members who are non-THR employees may be financially compensated for the member's time to review protocols and attend IRB meetings. Each IRB has at least one member who represents the perspective of research subjects. Also, per ANCC Magnet Recognition Program, each IRB has at least one member who is a nurse.

The IRB will have sufficient expertise to review the broad range of research in which THR commonly becomes involved, will be knowledgeable about all relevant regulatory requirements, and will remain impartial and objective in their reviews.

b. Appointment of IRB Members, Length of Service, and Duties.

Candidates for membership on the IRB may be identified through the recommendations of the THR Institutional Official, the IRB Chairperson, members, and administrative staff, and/or officials of THR Entities that conduct human subject research. Every effort is made to select personnel from a variety of disciplines, which represent the types of research proposals submitted for review and approval.

- (i) The IRB must comply with the membership requirements of DHHS regulations at [45 CFR 46.107](#) and FDA regulations at [21 CFR 56.107](#). Members of the IRB are appointed in accordance with the DHHS and FDA regulatory requirements and local policies and procedures, and with the concurrence of the THR Institutional Official.
- (ii) Each member will be appointed to the IRB for a term not to exceed two years. A member's term may be extended for additional two year terms without limitation.
- (iii) Members vote to approve, require modifications in, disapprove, or defer research submitted to the IRB. Members are expected

to attend IRB meetings on a regular basis (50 percent of all convened meetings), serve as primary and secondary reviewers for research within their areas of expertise, and serve as Members are also expected to conduct expedited reviews on behalf of the IRB when so designated by the IRB Chairperson.

- (iv) Scientific members will have experience in research involving human subjects, and will be recruited from among medical staff members of THR hospitals or from the community.

Non-scientific members will have training in human rights issues and/or ethical or legal issues considered to be relevant to human subject research, and will be recruited from among the personnel of THR Entities.

Unaffiliated community-based members will be non-scientists without any other THR affiliation and will be recruited from the community of Dallas, Fort Worth, Arlington, and other areas in the service area of THR hospitals.

- (v) Any member of the IRB may be removed for scientific misconduct, conflict of interest, or argumentative behavior such that approval of research is difficult or impossible.
- (vi) The IRB will include a THR attorney as a Continuing Consultant (i.e., non-voting member, see item [“e”](#) below).

c. Appointment of IRB Chairperson, Length of Service, and Duties.

The IRB will have a Chairperson who will be a respected professional, who has the qualifications of a scientific member of the IRB, is concerned about human rights and ethical issues, and is well-informed concerning regulations relevant to the involvement of human subjects in research.

The Chairperson of the IRB is appointed by the IRB in accordance with THR’s processes and the DHHS and FDA regulatory requirements.

The IRB Chairperson will be appointed to a two-year term, renewable for consecutive two-year terms without limitation.

The IRB Chairperson has the following duties:

- Conduct each meeting in an orderly manner. The Chairperson is responsible for chairing the meeting, conducting business so that each proposal is fairly and completely reviewed, seeing that

the Board reaches a decision on the disposition of each proposal and ensuring that these decisions are communicated to the individuals who submitted the proposal.

- Review and approve research utilizing expedited review procedures in accordance with DHHS and FDA regulations.
- Review, as needed and as delegated by the IRB in appropriate circumstances, responses from investigators to determine if they respond sufficiently to the IRB's concern to allow approval under expedited review procedures and without being returned to the fully convened IRB.
- Appoint qualified IRB members to review and approve research utilizing expedited procedures in accordance with DHHS and FDA regulations.
- Sign correspondence on behalf of the IRB.
- When applicable, appoint a Vice Chairperson, with approval of the THR Institutional Official, and seek consultation and/or agreement by other members of the IRB. The Vice Chairperson will be a scientific member of the IRB who will assume the responsibilities of the Chairperson during any period of the Chairperson's absence.
- Assure IRB policies and procedures are reviewed at least annually to confirm current compliance with all Federal, State, and local requirements for the protection of human subjects.

The Chairperson may be removed from an IRB by THR due to scientific misconduct, conflict of interest, obstructive behavior towards THR Administration, and/or interference with the directives of the THR Institutional Official.

- d. Alternate IRB Members.** The IRB, at its discretion, may recruit alternate members to substitute for certain regular members of the IRB whose input to the deliberations at meetings has unique importance. These members may include scientists, or non-scientist members familiar with the protection of human subjects. Alternate members must be listed on the IRB's official membership roster, which must specify which member (or members) the alternate is qualified to replace. (Note: Although an alternate may be qualified to replace more than one regular member, only one such member may be represented by the alternate at any convened meeting.)

Alternate members will have voting rights, except that they may not vote at meetings attended by their respective regular members. Alternate members will be included in determining or establishing quorum at meetings when their respective regular members are absent, but not when those regular members are present.

Procedures for appointment, terms of appointment, length of service, and duties are exactly as for regular IRB members. IRB members may nominate alternate members.

- e. Continuing Consultants to the IRB.** At its discretion, the IRB may recruit Continuing (non-voting) Consultants (sometimes referred to as “non-voting or ex officio” members) whose presence at the meetings would aid the IRB in conducting its duties. Continuing Consultants may be recruited from personnel at THR Entities or facilities as the IRB deems appropriate. Continuing Consultants may take part in all meetings of the IRB, participate in IRB discussions, and make recommendations to influence IRB determinations. However, Continuing Consultants may not vote on IRB determinations. Continuing Consultants will not be included in determining or establishing quorum at IRB meetings. Continuing Consultants will be selected by the majority of the members of the IRB or through agreements with THR affiliate Institutions. The duration of their appointment will not be limited.
- f. Ad Hoc Consultants.** At its discretion, the IRB may recruit scientist or non-scientist Ad Hoc Consultants who have special expertise that can assist the IRB in its deliberations. Ad Hoc Consultants may be recruited from inside or outside THR. Their special expertise shall qualify them to serve as ad hoc reviewers for specific projects or protocols identified by the IRB. Ad Hoc Consultants may have access to all documents submitted to the THR IRB relevant to the specific project under review, may participate in the deliberations and make recommendations, but may not vote with the THR IRB. The identity of such Ad Hoc Consultants may be kept confidential to the extent permitted by DHHS and FDA regulations and THR policies and procedures.
- g. Legal Counsel.** The IRB will include a THR staff attorney as a Continuing Consultant (i.e., non-voting member). In this capacity, the attorney serves as Counsel to the IRB in fulfilling its function to protect the rights and welfare of human subjects.
- h. IRB Membership Requirements.** In compliance with Federal regulations at [45 CFR 46.107](#) and [21 CFR 56.107](#), the IRB must satisfy the following requirements:

 - (i) The IRB will have at least five members;
 - (ii) IRB members will possess varying backgrounds to promote complete and adequate review of research activities commonly conducted at THR and Institutions for which the THR IRB is the designated IRB;

- (iii) IRB members will be sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects;
- (iv) IRB members will include persons able to ascertain the acceptability of proposed research in terms of Institutional commitments, regulations, applicable law, and standards of professional conduct and practice;
- (v) IRBs will consist of qualified persons of both sexes;
- (vi) The IRB will not consist entirely of members of one profession;
- (vii) The IRB will include at least one member whose primary expertise is in a scientific area;
- (viii) The IRB will have at least one member whose primary concerns are in non-scientific areas; and
- (ix) The IRB will include at least one member who is not otherwise affiliated with THR and who is not part of the immediate family of a person who is affiliated with THR or other Institutions for which the THR IRB is the designated IRB.

- i. Conflicts of Interest.** No IRB member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members, including the Chairperson, who have conflicting interests, are required to disclose such interests and to absent themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences are recorded in the meeting's minutes.

While some IRB members also conduct research, it remains the member's ongoing responsibility to disclose any real or apparent conflicting interests to the IRB and to absent themselves appropriately from any IRB deliberations on which they may be conflicted. For this reason, a [Conflicts of Interest Declaration \(Form COI-3\)](#) must be completed by each IRB member prior to each meeting.

- j. Initial Training, Continuing Education, and Professional Development of IRB Members.** Upon receiving an appointment to the IRB, a member receives comprehensive reference materials (including these operating procedures) necessary to review research from an ethical and regulatory perspective. New members should have the opportunity to observe several IRB meetings before they are assigned studies to review. Members will periodically be provided with continuing education opportunities within THR or at

neighboring Institutions, and resources will be made available each fiscal year for one or more IRB members to attend national or regional human subject protection meetings. In order to be seated, new and continuing IRB members must complete such training as the THR Institutional Official deems warranted.

- k. Evaluation of IRB Chair, Vice Chair(s) and IRB Members.** The IRB Chair, Vice Chairs and IRB Members will undergo evaluations annually. The IRB Chair and Vice Chair's will be evaluated by the Institutional Official (IO) or designee and the IRB Member's will be evaluated by the IO or designee. New members to the Board (including IRB Chairs/Vice Chairs) will be evaluated at the end of their first 90 days and then again at the time of annual review. A formal evaluation form (tool) has been developed for the IRB Chair and Vice Chair(s) and for the IRB Members to assist with conducting the annual evaluations. Feedback related to the evaluations will be provided either in person and/or through a letter to the IRB Chair/Vice Chair(s) or the IRB members depending upon the review outcome. The results of the individual evaluations for the IRB Chair/Vice Chair evaluation (completed by the IO) will be shared with the IRB Manager, Director of Research Administration,, and the EVP of Population Health Management/President Institute for Population Health. The results of the IRB Member evaluations will be shared with the IRB Manager, Director of Research Administration, and the EVP of Population Health Management/President Institute for Population Health. The IO or designee will have the opportunity to recommend that the member/Chair/Vice Chair continue on the Board or recommend that they do not continue. If a separation (discontinuation of membership) is recommended, the rational/reasons as noted on the evaluation form will be discussed with the IO or designee and the IO or designee will make the final determination. Aggregate (combined) information from all evaluations will be shared with RACC (Research Activities Compliance Committee) and THR Compliance and will be used to identify areas of strength and to focus on areas of improvement.
- l. Telephonic and Video Conferencing:** IRB Members may participate in IRB meetings via telephonic and/or video conferencing.

Chapter 7. IRB Administrative Support

DHHS regulations at [45 CFR 46.103\(b\)\(2\)](#) require that THR provide the IRB with sufficient meeting space and staff to support the IRBs' review and recordkeeping responsibilities.

- a. Resource Allocation.** The THR Institutional Official has ultimate responsibility for confirming the protection of human subjects in research conducted within THR. To this end, the THR Institutional Official will see that THR supports the IRBs' review and recordkeeping responsibilities.
- b. Reporting Lines and Supervision.** All IRB administrative staff ultimately report to and take direction from the THR Institutional Official in coordination with the IRB Chairperson.
- c. Initial Training, Continuing Education, and Professional Development of IRB Staff.** THR is required under its OHRP Assurance (FWA) to have a plan to provide education about human subject protections for IRB staff. All IRB staff must complete training as determined by the THR Institutional Official.
- d. IRB Professional Staff Duties.** IRB Professional Staff are responsible for the following IRB support functions:
 - (i) Maintaining the official roster of IRB members;
 - (ii) Scheduling IRB meetings;
 - (iii) Distributing pre-meeting materials with sufficient time to allow IRB members an opportunity to review them in preparation for the meeting;
 - (iv) Compiling the minutes of IRB meetings in compliance with regulatory requirements;
 - (v) Maintaining all IRB documentation and records in accordance with regulatory requirements;
 - (vi) Assisting new IRB members in completing orientation procedures and meeting required education standards;
 - (vii) Securely and properly archiving all IRB records;
 - (viii) Facilitating communication between investigators and the IRB;
 - (ix) Tracking the progress of each research protocol submitted to the IRB;
 - (x) Maintaining a computerized database for tracking purposes and logging incoming information into the database;

- (xi) Serving as a resource for investigators on general regulatory information, and providing guidance about forms and submission procedures;
- (xii) Drafting reports and correspondence to research investigators on behalf of the IRB or IRB Chairperson regarding the status of the research, including conditions for initial or continuing approval of research and responses to reports of reportable adverse events or unanticipated problems (refer to Chapter 9 for specific information);
- (xiii) Drafting reports and correspondence directed to research officials, Federal officials, and others on behalf of the IRB, IRB Chairperson or the THR Institutional Official;
- (xiv) Maintaining quality control of IRB support functions;
- (xv) Assisting in evaluation, audit, and monitoring of human subject research as directed by the IRB and the THR Institutional Official;
- (xvi) Reading through incoming applications and checking them for completeness. Checklists are used to ensure that each and every item is addressed and comments on discrepancies are noted accordingly.;
- (xvii) Reading through the informed consent document to ensure it is written at a level that is easily understandable for the subjects that will be recruited and that the appropriate consent form has been used (e.g., for research involving vulnerable subjects or non-English speaking subjects); and

Ultimately, IRB professional staff are responsible for documenting that IRB activities and decisions fully satisfy all regulatory requirements. Thus, such staff must have a detailed, working knowledge of relevant regulatory requirements.

- e. IRB Support Staff Duties.** IRB support staff supplement the function and operation of the IRB under the direction of appropriate IRB professional staff.

Chapter 8. IRB Recordkeeping and Required Documentation

Federal regulations require that THR implement written policies and procedures to govern the operations and direct the activities of its IRB. This IRB Policies and Procedures document satisfies that requirement.

IRB Staff are responsible for developing and implementing procedures for efficient document flow and maintenance of all IRB records.

- a. Record Retention.** IRB records will be retained for no less than ten years, and research records will be retained by THR for no less than ten years after the completion of the research. See Table 17-III Record Retention Schedule – Human Subject Research for a detailed description of record retention time frames located as a separate document on the IRB website/policy page and THR PolicyConnect. Federal regulations at [21 CFR 56.115\(b\)](#) and [45 CFR 46.115\(b\)](#), require IRB records be retained by the IRB for no less than three years and research records will be retained by THR for not less than three years after the completion of the research.
- b. Access to IRB Records.** All IRB records will be kept secure in locked filing cabinets, locked storage rooms or the eIRB. Ordinarily, access to IRB records is limited to the IRB Chairperson, IRB members, IRB staff, the THR Institutional Official, the THR Chief Compliance Officer, and officials of Federal and State regulatory agencies, including OHRP and FDA. Research investigators will be provided reasonable access to files related to their research. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IRB Chairperson or designee.
- c. IRB Records.** Refer to Record Retention Schedule – Human Subject Research (Table 18-III) located as a separate document on the IRB website/policy page and THR PolicyConnect
- d. IRB Membership Rosters.** Any changes in IRB membership will be reported promptly to OHRP/FDA.

All IRB membership rosters will include the following information.

- (i) Names of IRB members;
- (ii) Names of alternate members and the corresponding regular member(s) for whom each alternate may serve;
- (iii) Earned degrees and specialties of each member and alternate, if applicable, sufficient to describe each member's chief anticipated contribution to IRB deliberations;

- (iv) The representative capacity or specialties (e.g., scientific specialty cardiology, non-scientific specialty-chaplain) of each member or alternate;
- (v) Any employment or other relationship with THR or a THR Entity (e.g., full or part time employee, stockholder, member of governing board, paid or unpaid consultant);
- (vi) Representative capacities or specialties in terms of the vulnerable populations (e.g., prisoner representative), if any, each member is knowledgeable about or experienced in working with; and
- (vii) Indications of experience sufficient to describe each IRB member's chief anticipated contributions.

- e. Education and Training Records.** THR is required under its OHRP Assurance to have a plan to provide education about human subject protections for research investigators and IRB members and staff.

Research Investigator Education. At a minimum, all research investigators must complete the education program provided by THR. Refer to the THR Policy, Training Requirements for IRB Members, IRB Office Staff, Research Investigators and Research Study Staff for detailed information regarding educational requirements and additional training information. The Policy can be accessed via the [THR IRB website](#).

IRB Member and Staff Education. IRB members and staff must complete training as determined by the THR Institutional Official.

Training Records. The IRB will maintain accurate records listing research investigators, IRB members, IRB staff and research staff who have fulfilled THR's human subject protection training requirements. Such records will be available for review by the THR Institutional Official as a part of compliance monitoring activities.

- f. IRB Correspondence.** IRB Staff will maintain accurate records of all correspondence to and from the IRB.
- g. IRB Research Application (Protocol) Files.** The IRB will maintain a separate file for each research application (protocol) that it receives for review.

The IRB research application (protocol) file should contain the following materials:

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

- (i) The IRB Research Application (Protocol) Form (included via the THR eIRB system. All researchers and staff should have access to this electronic system.);
- (ii) Documentation of type of IRB review;
- (iii) The IRB-approved informed consent document, with the beginning and ending dates of the current approval period clearly date stamped on at least the first page;
- (iv) Copies of all research proposals reviewed and scientific evaluations of the proposed research, if any;
- (v) Applications for Federal support, if any;
- (vi) Sponsor or cooperative group protocols and sample informed consent documents, if any;
- (vii) Advertising or recruiting materials, if any;
- (viii) Applications for protocol amendments or modifications, if any;
- (ix) Continuing review progress reports and related information;
- (x) Reports of unanticipated problems involving risks to subjects or others, if any;
- (xi) Reported adverse events, reportable adverse events, and unanticipated problems occurring within THR Entities (or involving THR employees or agents or in which THR is engaged) and reported to any regulatory agency (refer to Chapter 9 for specific information), if any;
- (xii) Reported and reportable external adverse events, external unanticipated problems and/or safety reports received from sponsors or cooperative groups, if any;
- (xiii) DSMB reports, if any;
- (xiv) All IRB correspondence to and from research investigators;
- (xv) All other IRB correspondence related to the research;
- (xvi) Documentation of all IRB review and approval actions, including initial and continuing convened (full) or expedited IRB review;
- (xvii) Documentation of Project Closeout. (It is the policy of the THR IRB to administratively close and return to the Principal Investigator any new research application when additional information requested by the IRB is not submitted within a 90-day period.); and
- (xviii) Documentation of statements of significant new findings provided to subjects.
- (xix) Protocol deviations/violations.

IRB files will be kept per Table 18-III, THR Human Subject Research Records and Documents - Record Retention Schedule located as a

separate document on the IRB website/policy page and THR PolicyConnect.

- h. IRB Database.** The THR Institutional Official will provide the IRB with access to a centralized IRB research (protocol) tracking database.

At a minimum, the database will include the following information:

- (i) Title of the Research (Protocol);
- (ii) Name of Principal Investigator;
- (iii) Funding Source (if any);
- (iv) Date of Initial Approval;
- (v) Date of Most Recent Continuing Approval;
- (vi) End of Current Approval Period;
- (vii) Type of Review (Expedited or Convened Review); and
- (viii) Current Status (Under Review, Approved, Suspended, Closed).

- i. Documentation of Exemptions.** Identification of research activities that are exempt from the human subject regulations requires a level of expertise and is not left to individual investigators.

All exemptions claimed for research conducted at THR or by employees or agents of THR must be verified by the Chairperson of the THR IRB, or an individual designated by the Chairperson.

In reviewing exemption requests, the IRB must elicit enough information from the investigator to ascertain whether the claimed exemption really applies.

Documentation of verified exemptions consists of the reviewer's written concurrence in the IRB Research Application File that the activity described in the investigator's application for exempt research (included in the THR eIRB system, which all researchers and staff should have access to this electronic system) satisfies the conditions of the cited exemption category.

The exemptions do not apply to research involving prisoners. The exemptions do apply to research involving pregnant women, fetuses, and neonates.

The categories of exempt research are stipulated in the Federal Policy (Common Rule) and in DHHS regulations at [45 CFR 46.101\(b\)\(1-6\)](#). The most frequently applicable exemptions include the following:

Exempt Research in Educational Settings. Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations in accordance with [45 CFR 46.101\(b\)\(1\)](#).

- (i) This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed.
- (ii) Even if the research is exempt, the investigator has an ethical obligation to respect and safeguard students' rights and welfare.

Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at [45 CFR 46.101\(b\)\(2\)](#).

- (i) When the subjects are **adults**, this exemption applies **UNLESS**: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); **AND** (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. **NOTE**: The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.
- (ii) This exemption applies to research involving **children**, **EXCEPT** that: (a) research involving survey or interview procedures with children is **NOT EXEMPT**; and (b) research involving observation of the public behavior of children is **NOT EXEMPT** if the investigator participates in the actions being observed.
- (iii) If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) Federal statutes require confidentiality without exception. (**NOTE**: Condition (b) regarding Federal statutes rarely applies. The IRB will consult with OHRP if it receives an exemption request based on

absolute confidentiality under a Federal statute.) If not exempt under the conditions described above, the IRB may often utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.

Exempt Use of Existing Materials. Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

- (i) Such research may be exempt under DHHS regulations at [45 CFR 46.101\(b\)\(4\)](#) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects.
- (ii) If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.
- (iii) However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

- j. Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article.** FDA regulations at [21 CFR 50.23](#) permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician, not otherwise involved in the research, certify in writing that (i) the subject is confronted with a life threatening emergency; (ii) informed consent cannot be obtained because of an inability to communicate; (iii) time is not sufficient to obtain consent from the subject's legally authorized representative; and (iv) there is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the life of the subject.

This written certification must be submitted to the IRB within 5 working days of the use of the test article. IRB staff is responsible for maintaining this documentation in IRB records. Refer to Table 17-I for reporting requirements.

- k. Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test Article.** FDA regulations at [21 CFR 56.104\(c\)](#) permit the emergency use of a test article without IRB review. Emergency use is defined as use of a test article on a human subject in a life threatening situation in which no standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval ([21 CFR 56.102\(d\)](#)). All of the following conditions must be met for this type of emergency use: (i) an individual is in a life-threatening situation; (ii) no standard acceptable treatment is available; (iii) there is insufficient time to obtain IRB approval; and (iv) the emergency use must be reported in writing to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB. IRB staff is responsible for maintaining this documentation in IRB records.
- l. Documentation of Expedited Reviews.** Expedited IRB review procedures may be employed for (i) minor changes in previously approved research during the specified approval period, or (ii) initial or continuing review of research falling within specific categories published in the Federal Register (45 CFR 46.110 and 21 CFR 56.110). Expedited reviews are conducted by the IRB Chairperson or a qualified IRB member designated by the Chairperson.

Documentation. Documentation for expedited review and approval consists of the reviewer's written concurrence in the IRB Research Application File that the activity described in the investigator's application for expedited review (included in the THR eIRB system, which all researchers and staff should have access to this electronic system.) satisfies the conditions (i) for a minor change, or (ii) of the cited expedited review category.

FDA/DHHS Specified Categories. It is the policy of the IRB to provide an expedited review of research activities that fall within the FDA/DHHS specified categories and involve no more than minimal risk to human subjects and that therefore may not require review by the convened IRB. The IRB Chairperson or his or her designee may perform expedited reviews and decide whether to approve, request additional information or submit the application to the fully convened IRB. If approved by either the Chairperson or his or her designee, the activity will be reported to the IRB at the next fully convened meeting. The expedited reviewer may not disapprove any research activity. The research activity may be disapproved only after review by the fully convened IRB.

Informed Consent Applies. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review.

Request for Full IRB Review. Any IRB member may request that an activity that has been approved under the expedited review procedure be reviewed by the fully convened IRB in accordance with non-expedited procedures. A vote of the IRB membership (with a majority of IRB members present, including at least one non-scientist) will be taken concerning such a request, which may be (a) for more information, (b) to request modifications in the research, or (c) to disapprove the research. A majority vote of IRB members present will decide the issue.

m. Documentation of Convened IRB Meetings—Minutes. IRB staff will compile the minutes of IRB meetings. The following specific information will be recorded in the meeting minutes, when applicable:

- (i) Attendance;
- (ii) Quorum requirements;
- (iii) Actions taken by the IRB on the initial or continuing review of research; review of protocol or informed consent modifications or amendments; unanticipated problems involving risks to subjects or others (refer to Chapter 9); adverse event reports (refer to Chapter 9); reports from sponsors, cooperative groups, or DSMBs; reports of continuing noncompliance with the human subject regulations or IRB determinations; suspensions or terminations of research; and other actions. The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB;
- (iv) Votes on these actions;
- (v) The basis for requiring changes in or disapproving research;
- (vi) Summary of controverted issues and their resolution;
- (vii) Required IRB findings and determinations; and
- (viii) A list or reference to an electronic listing of research approved since the last meeting utilizing expedited review procedures.

The IRB meeting minutes will be submitted to the members of the IRB for review and approval. On approval, the minutes will be executed by the Chairperson, on behalf of the IRB.

n. Attendance at IRB Meetings. IRB minutes will list attendance as follows:

- (i) Names of members present;
- (ii) Names of absent members;
- (iii) 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;
- (iv) Names of non-voting members and consultants present;
- (v) Name of investigators present; and
- (vi) Names of guests present.

o. Quorum Requirements and Voting at IRB Meetings. IRB minutes will include a statement of Quorum Requirements based on the following standards:

- (i) A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting. Should the quorum fail during a meeting (e.g. loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.
- (ii) Members may be present in person or via telephone or audio-visual teleconference (webinar).
- (iii) IRB minutes will document the number of members voting for, against, and abstaining;
- (iv) Members absenting themselves due to conflicting interests may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining); and
- (v) No individual who is not listed on the official IRB membership roster may vote with the IRB.

p. Actions Taken by the Convened IRB. IRB minutes will include all actions taken by the convened IRB and the votes underlying those actions. IRB actions for initial or continuing review of research include those listed below. These actions will also be provided in writing to investigators in the form of a written communication from the IRB which includes, at minimum, the following information (where appropriate): investigator's name, title of study, IRB number, level of risk as determined by the IRB, approval date, continuing review interval, and changes to the materials submitted in order to secure approval.

- (i) Approved as submitted, with no changes (or no additional changes). The research may proceed.
 - (ii) Approvable with minor changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol approved by the designated reviewer. IRB staff and non-voting members of the IRB may not approve these changes. Such changes require the approval of a voting IRB member.
 - (iii) Tabled. Approvable with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
 - (iv) Deferred. Pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
 - (v) Disapproved. The IRB has determined that the research cannot be conducted at THR or by employees or agents of THR or in which THR would be considered engaged.
 - (vi) Approved contingent upon receipt of any ancillary information or documents requested by the IRB. IRB Staff (non-voting) may approve responses to requests that involve change in study personnel, IRB fee payment and changes to study that are deemed administrative or clerical.
- q. Substantive Conditions (or Modifications)** would involve (a) More than minimal risk to the research subject or (b) Major changes in the direction of the study that may substantially change the purpose of the study or the risk/benefit ratio, or (c) in the Board's view would likely impact a participant's decision to remain in the research, or (d) questions, clarifications or requests for information that the IRB does not possess at the time of review related to criteria for approval (45 CFR 46.111 and/or 21 CFR 56.111) .
NOTE: Requests for clarification to confirm that an understanding is correct are not substantive modifications (even if they are in regard to criteria for approval).
- r. The Basis for Requiring Changes in or Disapproving Research.**
The minutes of IRB meetings will include the basis for requiring changes in or disapproving research. This information will also be provided in writing to the investigator, who will be given an opportunity to respond in person or in writing.

- s. Summary of Controverted Issues at Convened Meetings.** The minutes of IRB meetings will include a summary of the discussion of all controverted issues and their resolution.
- t. Required IRB Findings and Determinations.** The following specific IRB findings and determinations will be documented in IRB meeting minutes, including protocol-specific information justifying each finding or determination:
- (i) The level of risk of the research.
 - (ii) The approval period for the research, including identification of research that warrants review more often than annually.
 - (iii) Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
 - (iv) Justification for waiver or alteration of informed consent, addressing each of the 4 criteria at [45 CFR 46.116\(d\)](#). Briefly, the criteria that the IRB must find and document are: (1) the research involves no more than minimal risk to subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.
 - (v) Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at [45 CFR 46.117\(c\)](#) and 21 CFR 56.109(c).
 - (vi) For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses and neonates, addressing each of the criteria specified under [Subpart B](#) of the DHHS human subject regulations.
 - (vii) For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under Subpart C of the DHHS human subject regulations. The IRB Chairperson is responsible for providing certification of the IRB's findings to OHRP.
 - (viii) For DHHS-supported research and for FDA-regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under [Subpart D](#) of the DHHS or FDA human subject regulations. The IRB Chairperson is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts.

- (ix) 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, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
- (x) Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special [45 CFR 46.101\(i\)](#) DHHS waiver or the FDA exception at [21 CFR 50.24](#).
- (xi) IRB minutes must document the rationale for significant risk/non-significant risk device determinations.
- (xii) IRB minutes must document IRB requested clarifications or modifications are substantive or not substantive in nature.

For research reviewed under an expedited review procedure, the above mentioned findings and determinations in items iv, v, vi, vii and viii will be documented by the IRB Chairperson or other designated reviewer elsewhere in the IRB record.

Chapter 9. Procedures for IRB Review

All human subject research conducted at THR or by THR's employees or agents or in which THR is defined as engaged must be prospectively reviewed and approved by the THR IRB. No human subject research may be initiated or continued at THR or by THR's employees or agents or in which THR is defined as engaged without prospective approval of a THR IRB.

- a. Review by the Convened IRB.** Federal regulations, the Federal Policy (Common Rule) for the Protection of Human Subjects, and FDA regulations require that the IRB conduct initial reviews, continuing reviews, proposed protocol changes, and/or review of reports of unanticipated problems or of serious or continuing non-compliance of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review (see item ["e"](#) of this Chapter).

A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting.

- b. Initial Review by the Convened IRB.** Except for unusual circumstances, at least one week prior to the convened meeting, IRB members will be provided detailed initial review materials describing the research in order to discuss the protocol adequately and determine the appropriate action during the convened review. These materials include:
- the IRB research (protocol) application form (which includes a lay language protocol summary, information about subject recruitment and selection, the research plan, risks and benefits, privacy and confidentiality protections, safety monitoring, informed consent procedures, and protections for vulnerable subjects);
 - the proposed informed consent document(s);
 - any recruitment materials (including advertisements to be seen or heard by potential subjects);
 - Information related to the industry-sponsored contract and/or budget (if applicable); and
 - any other information relevant to the approval criteria described in the regulations.

In addition, primary and secondary reviewer materials include:

- the full industry protocol or investigator's project description;
- clinical investigator's brochure/instructions for use or manual of operations (if applicable);
- the full grant application or proposal (without attachments) for any Federally supported research on which THR or any THR hospital is the direct awardee; and
- any other information relevant to the approval criteria described in the regulations.

For HHS-supported multicenter clinical trials, the IRB should receive and review a copy of the HHS-approved sample informed consent document and the complete HHS-approved protocol, if they exist.

All study materials can be accessed electronically by all IRB members via the eIRB submission system.

- c. Continuing Review by the Convened IRB.** The IRB is required to conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Continuing reviews will be conducted by a convened meeting of the IRB unless the research falls into one or more of the categories appropriate for expedited review (see item ["e"](#) of this Chapter).

Except for unusual circumstances, at least one week prior to the convened meeting, IRB members will be provided with detailed continuing review materials sufficient to conduct substantive and meaningful reviews. These materials include:

- the currently approved informed consent document
- the IRB continuing review application form, which includes a summary of the research, a status report on the progress of the research, number of subjects enrolled and withdrawn, problems and adverse events, unanticipated problems, relevant recent literature, and other relevant information.

In addition, primary and secondary materials include:

- the full industry protocol or investigator's project description;
- clinical investigator's brochure/instructions for use or manual of operations (if applicable);
- the full grant application or proposal (without attachments) for any Federally supported research in which THR or any THR hospital is the direct awardee; and
- any other information relevant to the approval criteria described in the regulations.

All study materials can be accessed electronically by all IRB members via the eIRB submission system.

- d. Review of Protocol Changes by the Convened IRB.** Except for unusual circumstances, at least one week prior to the convened meeting, the IRB members will be provided detailed review materials describing the protocol changes in order to discuss the amendment(s) adequately and determine the appropriate action during the convened review. These materials include;
- the amendment application form;
 - relevant materials that describe the change(s) (i.e., summary of changes) or need amending due to the change(s) (i.e., informed consent form); and
 - any other information pertaining to the approval criteria described in the regulations.

When applicable, additionally the primary and secondary reviewer materials include:

- the full industry protocol or investigator's project description;
- clinical investigator's brochure/instructions for use or manual of operations;
- the full grant application or proposal (without attachments) for any Federally supported research on which THR or any THR hospital is the direct awardee;
- and any other information relevant to the approval criteria described in the regulations.

All study materials can be accessed electronically by all IRB members via the eIRB submission system.

- e. Review of Reports of Unanticipated Problems by the Convened IRB.** Except for unusual circumstances, at least one week prior to the convened meeting, the IRB members will be provided detailed review materials describing the unanticipated problem(s) in order to discuss the submission adequately and determine the appropriate action during the convened review. These materials include:
- the safety/other application form;
 - relevant additional materials that describe the unanticipated problem(s) (i.e., source documentation, report from sponsor) or need amending or reporting due to the unanticipated problem(s) (i.e., informed consent form, amendment application form); and
 - any other information pertaining to the approval criteria described in the regulations.

When applicable, additionally the primary and secondary reviewer materials include:

- the full industry protocol or investigator's project description;
- clinical investigator's brochure/instructions for use or manual of operations;
- and any other information relevant to the approval criteria described in the regulations.

All study materials can be accessed electronically by all IRB members via the eIRB submission system.

f. Review of Reports of Serious or Continuing Non-Compliance by the Convened IRB. Except for unusual circumstances, at least one week prior to the convened meeting, the IRB members will be provided detailed review materials describing the serious or continuing non-compliance in order to discuss the submission adequately and determine the appropriate action during the convened review. These materials include:

- the safety/other application form and/or other relevant IRB application form;
- relevant additional materials that describe the serious or continuing non-compliance (i.e., source documentation, report from sponsor) or that need amending or reporting due to the serious or continuing non-compliance (i.e., informed consent form, amendment application form);
- and any other information relevant to the approval criteria described in the regulations.

When applicable, additionally the primary and secondary reviewer materials include:

- the full industry protocol or investigator's project description;
- clinical investigator's brochure/instructions for use or manual of operations;
- the full grant application or proposal (without attachments) for any Federally supported research on which THR or any THR hospital is the direct awardee;
- and any other information relevant to the approval criteria described in the regulations.

All study materials can be accessed electronically by all IRB members via the eIRB submission system.

g. Use of Primary and Secondary Reviewers with Convened IRB Reviews. In accordance with FDA and OHRP guidance, the IRB may utilize a primary reviewer system to assist in the initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems or of serious or continuing noncompliance review of research by the convened IRB.

When utilized, the primary reviewers for above reviews, are considered the lead reviewers for research proposals assigned to them. They are responsible for (i) being thoroughly versed in all details of the research; (ii) conducting an in-depth review of the research using the IRB Reviewer Forms; and (iii) leading the discussion of the research at the convened meeting. The secondary reviewers for above reviews are also responsible for (i) being versed in the research methodology and other aspects of the research; (ii) conducting an in-depth review of the research using the IRB Reviewer Forms.(iii) discussing the protocol at the convened IRB meeting. At least one week prior to the convened meeting, as a general rule, the primary and secondary reviewers must be provided with all the documents listed in [paragraphs \(b\)](#), (c), (d) (e) and (f) above.

Upon request, the entire IRB file will be available to all IRB members, and all IRB members will be afforded full opportunity to discuss each research proposal during the convened meeting. Also, upon request, any IRB member should have access to relevant IRB minutes prior to or during the convened IRB meeting. The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB. It is the responsibility of the primary and secondary reviewers to contact the IRB Office in regards to contacting individual investigators for clarification on any point during the review process.

h. Expedited Review of Research. DHHS regulations, the Federal Policy (Common Rule), and FDA regulations permit the IRB to review research through an expedited procedure if:

- (i) The research constitutes a minor change in previously approved research during the period for which approval is authorized. *or*
- (ii) The research is not greater than minimal risk and falls within the categories on the November 9, 1998 DHHS-FDA list of research eligible for expedited IRB review. Click on the following link to access those categories: [Expedited Categories.\\phdnas02\THRE\IRB\PoliciesandProcedures\Corporate Policy for Protection of Human Research Subjects\Proposed Changes\IRBTOC.doc - toc5](#)

Under an expedited review procedure, the IRB Chairperson or an experienced reviewer designated by the Chairperson may review and approve the research on behalf of the IRB. For initial and continuing reviews, reviews of protocol changes and reviews of

reports of unanticipated problems or of serious or continuing non-compliance reviews approved by expedited review, the IRB Chairperson or experienced reviewer designated by the Chairperson should receive all of the documentation listed in [paragraphs \(b\)-\(f\)](#) above. Refer to Chapter 4, section c, for Notice of Completion, Discontinuance of Project or Withdrawal of Exemption.

The IRB will keep all IRB members advised of research that has been approved under expedited procedures by listing or referencing an electronic listing of the research in the minutes of the next IRB meeting.

Documentation for expedited reviews maintained in IRB records will include the category and circumstances that justify using expedited procedures.

- i. Expedited Review of Minor Changes in Previously Reviewed Research.** Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in informed consent documents. No changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

The IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period.

A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in (i) the level of risks to subjects; (ii) the research design or methodology; (iii) the number of subjects enrolled in the research; (iv) the qualifications of the research team; (v) the facilities available to support safe conduct of the research; or (vi) any other factor which would warrant review of the proposed changes by the convened IRB.

- j. Expedited Initial and Continuing Review: Permitted Categories.** The IRB may utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk and falls within the categories on the November 9, 1998 DHHS-FDA list of research eligible for expedited IRB review. Click on the following link to access those categories: [Expedited Categories](#).

However, these categories do NOT apply to research involving prisoners.

The most frequently utilized expedited review categories are discussed below, and include research involving children as well as adult subjects.

Expedited Review of Research Involving Existing Materials.

Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes may be reviewed using expedited procedures. **NOTE:** The intent of the drafters was to define two categories here, each appropriate for expedited review.

- (i) Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.
- (ii) Non-exempt research involving materials that will be collected in the future for a non-research purpose (see below).

Prospective Use of “Existing” Materials. Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

- (i) Prospective studies using materials (data, documents, records or specimens) that will “exist” in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under DHHS regulations at [45 CFR 46.101\(b\)\(4\)](#) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated.
- (ii) However, the IRB may utilize **expedited procedures** to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes. The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.

Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies. The IRB may utilize expedited procedures to review the following:

- (i) Research on individual or group characteristics or behavior; or
- (ii) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Examples include, but are not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices.

This category also permits expedited review of non-exempt research using educational tests (cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or the observation of public behavior.

k. Revisions to Protocols. Revisions to a research protocol must be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents, which then supersedes the previous one.

I. Review and Reporting of Unanticipated Problems and/or Adverse Events.

(i) Overview

One of the charges of the IRB is to review “any unanticipated problems involving risks to subjects or others” (45 CFR 46.103(b)(5)(i) & 21 CFR 56.108(b)(1)).

An unanticipated problem involving risks to subjects or others (UP) is any unanticipated incident, event, or problem that is related to the conduct of the research and poses a risk to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research). Investigators, IRB staff, and IRB members are advised to fulfill

their functions described in this chapter based on this definition of an UP.

In accordance with Federal regulations, THR investigators are required to report UPs to the IRB.

UPs may include, but are not limited to the following categories:

- Adverse events that are unexpected and/or serious and related to the conduct of research regardless of whether they are on-site or off-site (see below for more detailed information)
- Subject complaints
- Medication or device errors
- Other errors in the conduct of the research
- Protocol deviations or violations (see paragraph O below)
- Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm to subjects
- Inappropriate disclosure of confidential or sensitive information
- Billing problems that pose unanticipated financial risk to subjects
- Any other incident or event that may qualify as an unanticipated problem involving risks to subjects or others

UPs may occur at non-THR sites, but could be relevant to the protection of research subjects at THR, and these UPs should also be reported to the THR IRB for review. If investigators are unsure as to whether a particular incident or problem represents an UP, they are expected to contact the Office of Research Compliance for guidance or to submit a report to the IRB for consideration.

(ii) Adverse Event Reporting

Adverse Events (AEs) are a category of unanticipated problems (UPs). Accordingly, the THR IRB requires that investigators report all AEs that qualify as unanticipated problems (UPs) to the IRB for review promptly.

OHRP guidance defines an AE as “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, of disease, temporarily

associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research." AEs encompass both physical and psychological harms. Note that most AEs occurring in human subjects are not UPs, and only a small portion meet the definition of a UP. Local AEs that do not qualify as UPs can be reported to the IRB periodically at the time of continuing review.

An AE qualifies as a UP if it meets all three of the following criteria:

1. Unexpected
 - a. The nature, severity, or frequency is not consistent with the known or foreseeable risk of adverse events described in the research documentation (e.g. protocol, investigators brochure, informed consent, package inserts) or the unexpected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.
2. Related or Possibly Related to the Research
 - a. Possibly related is defined as *"there is a reasonable threshold that the AE may have been caused by the procedures involved in the research."*
 - b. AEs may be caused by the 1) study procedures, 2) an underlying disease, disorder, or condition of the subject, or 3) other circumstances unrelated to the research or underlying disease, disorder or condition.
 - c. AEs at least partially caused by the study procedures (1) would be considered related or possibly related to the research. AEs caused solely by (2) or (3) would be considered unrelated to the participation in the research
3. Serious-suggests that the research places the subjects or others at a greater risk of harm than was previously known or recognized and:
 - a. results in death;
 - b. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
 - c. results in inpatient hospitalization or prolongation of existing hospitalization;
 - d. results in a persistent or significant disability/incapacity;
 - e. results in a congenital anomaly/birth defect; or
 - f. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

(examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Internal (local) AEs or SAEs that qualify as UPs must be reported promptly to the IRB **within 10 working days** after the investigator becomes aware of the event. (Refer to Table 17-II for reporting requirements).

If a study sponsor requires that an investigator report AEs or SAEs that do not meet the definition of a UP IRB staff will issue an acknowledgement that the report has been received by the IRB. However, this report will not undergo IRB review as it does not meet the IRB's reporting requirements.

Local SAEs occurring at THR sites that do not qualify as UPs can be reported to the IRB periodically at the time of continuing review in the Periodic Event Report Summary. External SAEs occurring at sites outside of THR that do not meet the definition of a UP do not need to be reported to the IRB.

Anytime after submission to IRB and until study closure: All external (non-local) AEs or related correspondence that:

- Change the study risks or benefits, OR
- Necessitates a modification to the THR-proposed/approved consent document(s), and/or the THR-proposed/approved application/protocol

must be reported **within 10 working days** after the investigator becomes aware of the event.

OHRP advises that it is neither useful nor necessary for reports of individual adverse events occurring in subjects enrolled in multicenter studies be distributed routinely to the local investigator and IRB. Individual external adverse events should only be reported to the THR IRB when a determination has been made that the event meets the criteria for an unanticipated problem. When an investigator receives an external adverse event report, he/she should review the report and assess whether it meets the following criteria:

- 1) unexpected;
- 2) related or possibly related to participation in the research, and

3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

For external AEs, the THR IRB will rely on the assessment of the Sponsor to determine if the AE qualifies as a UP (i.e. is it related/possibly related or is not related to the research).

External AEs/SAEs that do not meet the criteria of a UP (serious, related or possibly related, and unexpected) **do not** require reporting to the THR IRB.

For multicenter studies that are not monitored by a Data and Safety Monitoring Board /Data Monitoring Committee (DMC) or for multicenter studies whose DSMB reports are unavailable to the IRB, reports of AEs from other study sites must be submitted to the IRB within the above mentioned reporting procedures and time frames.

All Safety/Other reports of events that qualify as reportable must be submitted for IRB review via the eIRB with copies of any relevant documentation and reports attached (i.e., sponsor communication, source documentation), as applicable. The Principal Investigator should comprehensively describe the event in the context of the study protocol and provide his/her assessment of the event's relevance. Only events that are assessed as related or possibly related to the study require submission to and review by the IRB. If an event is assessed as not related, then submission to the IRB is not required.

Subject Deaths – Death is classified as a serious adverse event (SAE). However, in order for the death to qualify as unexpected problem (UP), and meet the IRB's reporting requirements, it must also be unexpected (not anticipated) and related or possibly related to the research (there is a reasonable threshold that the death may have been caused by the procedures involved in the research).

If death is a result of an underlying disease, disorder, or condition of the subject or if death is caused by other circumstances unrelated to either the research then the death does not meet the definition of a UP and does not require reporting to the IRB. Please refer to "Adverse Event Reporting" above.

Internal Deaths at THR Sites: If a death is assessed as unexpected and related or possibly related to the procedures involved in the research then it meets the definition of a UP. In order to ensure that subjects are afforded the utmost level of protection, internal deaths at

THR sites that are assessed as UPs **must be reported promptly within 24 hours of the PI/study staff awareness.** This includes deaths that occur during or within three months of having completed the study intervention when subjects are in follow-up.

External Deaths-External deaths at non-THR sites that are assessed as UPs should be reported within 10 business days of the PI/study staff awareness.

If a study sponsor requires that an investigator report deaths regardless of cause to the IRB, that do not meet the definition of a UP as defined above, IRB staff will issue an acknowledgement that the death report has been received by the IRB. However, the report will not undergo IRB review as it does not meet the reporting requirements.

In addition, the following **internal** events must always be reported to the IRB:

Normal Volunteers - The term “normal” refers to volunteer subjects who do not have the condition under study in a particular protocol and who are compared with subjects who do have the condition. Normal volunteers may also be used to study normal physiology and behavior.

UPs and SAEs for normal volunteers should be reported in the same fashion as subjects in a treatment group. UPs should be reported promptly to the IRB within 10 business days. Local deaths classified as UPs should be reported within 24 hours of the PI/study staff becoming aware of the death. SAEs, including deaths, that do not meet the criteria of a UP should be reported periodically at the time of continuing review using the Periodic Reportable Event Summary.

It should be noted that volunteers considered “normal” for research purposes are no more or less “normal” (in the commonly used sense of the term) than other study subjects. In fact, these subjects may not be “normal” in all respects. For example, patients with broken legs (if not on medication that will affect the study results) may serve as “normal” volunteers in studies of metabolism, cognitive development, and so on. Similarly, patients with heart disease but without diabetes may be considered “normal” in a study of diabetes complicated by heart disease. Because normal volunteers can generally expect no prospect of direct benefit from their participation in research, investigators must implement the highest protection standards to ensure their rights and welfare.

- **Human Gene Transfer Protocol** - For investigators who have received authorization from the FDA to initiate human gene transfer protocols, **serious adverse events must be immediately reported to the THR IRB** via Safety/Other reports in the eIRB, to the respective Biological Safety Committee (BSC) and NIH Office of Biotechnology Activities (OBA) (formally the Office of Recombinant DNA Activities). This is in accordance with Appendix M-I-C-4 of the NIH Guidelines. If applicable, follow-up information regarding the event(s) should be sent to each group. When submitting reports to the OBA, a copy of the [OBA Serious Adverse Experiences Reporting Form](#) should be used. Completed copies of the OBA form as well as the THR IRB Adverse Effect Report should be submitted to the THR IRB and BSC.

Reports submitted to the NIH OBA may be sent by: email to oba@od.nih.gov ; by fax to (301) 496-9838 or by mail to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, Maryland 20892-7985, Phone: (301) 496-9838.

- All unanticipated problems that, in the opinion of the investigator, may affect the risks of participation in the research.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the study materials (i.e., informed consent form) or would prompt other action by the IRB to ensure the protection of human subjects ([FDA Guidance-Adverse Event Reporting to IRBs-Improving Human Subject Protection](#)).

(iii) Reporting to Sponsor/Government

Investigators must also report adverse events to the study sponsor (as dictated by the study protocols) and/or to the FDA (in accordance with Federal regulations). Specifically, investigators must report any unanticipated adverse device effect (as defined in the IRB Glossary) to the sponsor and the IRB as soon as possible within 10 working days of the investigator learning of the effect (21 CFR 812.150 (a)(1)).

(iv) Reporting of DSMB/DMC and Safety Reports

In addition to submitting reports of all unexpected and/or serious and related adverse events, investigators of studies which are monitored by a DSMB should submit summary reports of all DSMB meetings to the IRB **within 10 working days** (Refer to Table 9-1).

Note that for multicenter studies that are not monitored by a DSMB or for multicenter studies whose DSMB reports are unavailable to the IRB, reports of adverse events from other study sites must be submitted to the IRB **within the above mentioned reporting procedures and time frames (Section ii).**

Investigational New Drug (IND) or other safety reports must be submitted to the IRB **within 10 working days** of their receipt by the PI. (Refer to Table 9-l).

All reports to the IRB must be submitted via the eIRB as a Safety/Other Report with copies of any relevant documentation and reports attached (i.e., sponsor communication).

(iv) Reporting of Other Types of Unanticipated Problems

Other types of UPs are incidents, experiences, or outcomes that are not adverse events that in the assessment of the investigator may represent an unanticipated problem or are problematic in nature. For example, suspension, hold or termination of study activities, inappropriate disclosure of confidential or sensitive information; medication or device errors; reduction in study resources that affects study conduct; complaint or concern from a subject that involves risk to the subject or others; or destruction of study records. Reporting does not include situations like a subject complaint regarding an overdue study payment.

Submit to the IRB all UPs that are:

- serious,
- unexpected and are
- related, probably related or possibly related to the study intervention(s)

within 10 working days after the investigator becomes aware of the event whether they occur at THR or at another study site.

In addition, investigators must promptly notify the IRB of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the IRB of which they become aware.

If a study sponsor requires that an investigator report events that do not meet the definition of a UP as defined above IRB staff will issue an acknowledgement that the report has been received by the IRB.

(vi) Changes to Study Due to an Unanticipated Problem

If the investigator is prompted by the study sponsor or IRB to revise the previously approved protocol and/or consent form in response to an unanticipated problem (i.e., adverse event), the proposed revisions should be submitted to the IRB via the eIRB as an amendment. In such a case, when the overall risk/benefit ratio of the study may be impacted by the event, no new subjects should be enrolled until the IRB has reviewed and approved the proposed revisions. If a temporary halt of enrollment poses significant problems, the investigator should immediately contact the Office of Research Compliance for guidance.

Regarding DSMB reports, if no study changes are proposed as a result of the report, the investigator should submit it via the eIRB as a Safety/Other Report. If changes to the study protocol, consent form, or investigator's brochure are made at the recommendation of the DSMB and or sponsor, the report should be submitted together with the proposed revisions via the eIRB as an amendment. When the overall risk/benefit ratio of the study may be impacted by the information in the report, no new subjects should be enrolled in the research until the IRB has reviewed and approved the changes recommended by the DSMB and/or sponsor.

(vii) Protecting Subject Privacy in Reporting

In order to protect the privacy of research participants, unanticipated problem reporting must not contain individually identifiable subject information. The investigator must remove all information, which directly identifies a subject from all materials before submitting them to the IRB.

If the AE pertains to a study, overseen by the Institutional Biosafety Committee (IBC), the IRB may share reports and any information generated from its review with the IBC.

(viii) Continuing Review

Each time a protocol undergoes continuing review, the IRB will review adverse events. For multicenter studies monitored by a DSMB, the continuation report should include a copy of the most recent DSMB Report.

IRB Chairperson Review. All such reports are reviewed by the IRB Chairperson or a qualified member of the IRB designated by the Chairperson. If the event is determined not to be related to the research, not serious, not unexpected and/or if the event does not require a change in the informed consent document, the reviewer documents this determination in writing. The report with documentation of the reviewer's determination is placed in the IRB Research

Application (Protocol) file and listed (or a reference to an electronic listing) should be in the minutes of the next IRB meeting.

Referral for Convened IRB Review. If, in the judgment of the IRB reviewer, the event may warrant more than a minor change in the protocol or informed consent process, the Chairperson will refer the event to the convened IRB for review. In the interim, the IRB Chairperson may require modification or suspension of research activities deemed necessary to eliminate apparent immediate hazards to subjects.

During the convened review, the IRB determines whether the research will be permitted to continue as proposed or whether changes are required. If the research will continue, the IRB also determines whether a consent form revision is required and to what extent re-consenting and/or subject notification about new information is warranted. The IRB has the authority to suspend the research if it has significant safety or other concerns.

Notice of IRB Determination(s). Regardless of the type of review (expedited or convened), the investigator is notified in writing of the IRB's determinations, even if no further action is necessary on the part of the investigator.

As warranted, it is the responsibility of the IRB Chairperson, or his/her designee, to provide prompt written notification to the THR Institutional Official and to relevant Federal Agencies, including OHRP and FDA (for FDA-regulated research) of any unanticipated problems involving risks to subjects or others, and of the resolution of those problems.

- m. Review of Sponsor or Cooperative Group Adverse Events or Safety Reports.** Generally, investigators are required to forward unanticipated problems or safety reports issued by sponsors or cooperative groups to the IRB within 10 working days of receipt (refer to section I for details). Each report should be accompanied by the completed IRB Safety/Other Reports, which is contained in the THR eIRB system. All researchers and staff should have access to this electronic system.

The IRB reviews and notifications of such reports are processed in the same manner as internal reports of unanticipated problems or serious adverse events (refer to previous section "I" of this Chapter for specific information)

- n. Review of Data and Safety Monitoring Board/Data Monitoring Committee Reports.**

Investigators are required to forward DSMB reports to the IRB within 10 working days of receipt that provide new information about the study.

DSMB reports that do not contain new information may be submitted at the time of continuing review. The review of DSMB reports is processed in the same manner as internal reports of unanticipated problems or adverse events (refer to section "I" of this Chapter for specific information).

When DSMBs are employed, the IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, 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. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

o. Reporting and Review of Protocol Deviations/Violations.

Non-emergent changes to the IRB-approved protocol (protocol deviation) that have been initiated or implemented without prior IRB approval are considered to be protocol violations.

Protocol violations that may affect subject rights, subject safety or welfare, the integrity of the research study and/or the subject's willingness to continue study participation must be reported to the IRB **within 10 working** days of the Principal Investigator becoming aware of the violation. Such submissions may be processed via an expedited review process or may be deemed appropriate for a full board (convened meeting) review.

Examples of violations are:

- incorrect intervention given
- enrollment of an ineligible subject,
- key safety procedure/lab not done or done outside of the time period to complete key procedure/lab,
- report of false information,
- informed consent not signed
- absence of consent or alteration of the consent process without prior written THR IRB approval is considered a protocol violation and must always be reported to the IRB
- the suspension or disqualification of an investigator is considered a violation that must always be reported to the THR IRB
- lapse in IRB approval
- a complaint from a research subject that indicates an unexpected risk or cannot be resolved by the study staff
- an audit finding, internal or external, that is directly related to activities described in the protocol and requires corrective action by the study staff must be reported

- any breach of confidentiality or privacy
- tests or study activity not completed
- missed or out of window visits or repetition thereof that in the opinion of the investigator, may affect subject safety, welfare, subject willingness to continue and/or data integrity
- loss of adequate resources to support continued research activities
- an unexpected natural disaster, such as an earthquake, that destroys records or disrupts scheduling

If a sponsor requests the reporting of a protocol violation that does not meet the above criteria and/or examples, it must be reported to the IRB. The IRB will determine if the submission is reportable.

Emergent Care. Except for emergency care, the PI may not conduct any research activities for an expired protocol without prior approval from the IRB. When subject safety is at issue, the PI may provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State or local law. In addition, there can be a change in the protocol if it is necessary to eliminate apparent immediate hazards to the subject. Any emergent change from the IRB-approved application made without prior IRB review must be reported within **5 working days** of its occurrence.

Refer to Table 17-II for investigator reporting requirements.

The section above (Review of Reports of Unanticipated Problems or Adverse Events) applies, if the protocol violation also involves reporting of respective information to the IRB.

Note that submission of recurring protocol violations and/or significant protocol violations may precipitate a research compliance review, which may result in the halting of research activities and/or reporting to the THR Compliance Officer, THR Legal and/or regulatory authorities.

- p. Research in Emergency Situations.** DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.
- q. Use of Subcommittees to Support IRB Activities.** The IRB may utilize subcommittees to support IRB review activities. At the discretion of the IRB

Chairperson, subcommittees may be appointed to perform expedited reviews or fulfill the duties of primary and secondary reviewers. The IRB Chairperson may also appoint subcommittees on an ad hoc basis to perform additional functions as needed.

- r. **Outcomes of IRB Review.** The IRB will notify investigators in writing of its determinations in the form of a memorandum from the IRB which includes, at minimum, the following information (where appropriate): investigator's name, title of study, IRB number, level of risk as determined by the IRB, approval date, continuing review interval, and changes to the materials submitted in order to secure approval. Except for (oral) acknowledgement (not approval) of emergency, one time use of investigational test articles, all IRB actions must be communicated in writing.

IRB Review Actions. IRB actions for review of research include the following:

- (i) Approved as submitted with no changes (or no additional changes). The research may proceed.
- (ii) Approvable with minor changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol is approved by the designated reviewer. IRB staff and non-voting members of the IRB may not approve these changes. Such changes require the approval of a voting IRB member.
- (iii) Tabled. Approvable with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
- (iv) Deferred. Pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
- (v) Disapproved. The IRB has determined that the research cannot be conducted at THR or by employees or agents of THR or in which THR would be considered engaged.
- (vi) Approved contingent upon receipt of any ancillary information or documents requested by the IRB. IRB Staff (non-voting IRB member) may approve responses to requests that involve change in study personnel, IRB fee payment and changes to study that are deemed administrative or clerical.

In addition to the Principal Investigator meeting requested stipulations and providing applicable IRB fee payment, final approval for initial submissions

will not be granted until the IRB is in receipt of the finalized Medicare information, contract(s)/grant(s) and any other information, as required.

- s. Expiration of Approval Period.** The IRB is required to conduct substantive and meaningful continuing review of research not less than once per year. Thus, the IRB approval period for research may extend no more than 365 days after the convened meeting or date at which the research was last approved.

The regulations permit no grace period and no exceptions to this one-year requirement. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities must stop. After expiration, all research activities must stop, including any research related interventions, recruitment, data collection, data sharing/reporting and analysis of identifiable data, and no new subjects may be enrolled. Research that continues after the approval period expires is research conducted without IRB approval. The THR IRB will provide a courtesy notice of study expiration to Principal Investigators prior to the study expiration date, however, it is the Principal Investigator's responsibility to monitor approval periods and ensure that continuing reports are filed timely for IRB review.

The IRB will automatically stop enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in expired research only when the IRB determines that continued involvement is in the best interest of the subjects. See section below titled Continuation of Study Activities Post Expiration for additional information. The IRB will send a courtesy notice informing the Principal Investigator of a lapse in approval; however, it is the Principal Investigator's responsibility to stop subject accrual pursuant to regulations.

If any data is collected during an approval lapse, it cannot be used for research unless approved by the IRB.

The PI should report to the IRB whether any research activities have occurred after the expiration date. If deemed appropriate by the IRB and/or PI, the PI must notify subjects that IRB approval for the study has lapsed and also notify the sponsor and/or funding source/agency of the lapse in IRB approval.

For an expired protocol, the IRB may require re-consent of affected subjects for continued study participation or documentation of written permission from the affected subjects for use of research data collected during the period of the approval lapse.

During an IRB approval lapse, the PI may submit new studies for approval and the IRB may review and approve such studies; however, the final approval (and release of the approved consent form) for any new study shall be contingent upon approval of either a continuing report or a final report (or administrative closure) for the expired study. A study that has been administratively closed can not be reactivated. Before any research activities can resume, a new protocol must be submitted for the expired study and approved by the IRB.

If a lapse in IRB approval extends beyond 90 days, the study shall be administratively closed unless closure is waived by the IRB Chairperson (or designee). The IRB Chairperson (or designee) will notify the Research Activities Compliance Council (RACC). Administrative closure shall be reported to the IRB, Entity Reviewer, and the Entity Chief Medical Officer. Report may also be made to the research study sponsor and Federal agencies.

Emergent Care. Except for emergency care, the PI may not conduct any research activities for an expired protocol without prior approval from the IRB. When subject safety is at issue, the PI may provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State or local law. In addition, there can be a change in the protocol if it is necessary to eliminate apparent immediate hazards to the subject. Any emergent change from the IRB-approved application made without prior IRB review must be reported **within 5 working days** of its occurrence.

Continuation of Study Activities Post Study Expiration.

The IRB Chairperson (or designee) may determine that continued research participation during the lapse in approval is in the best interest of the individual subjects (such as to avoid creating an overriding safety concern or ethical issue). If the IRB Chairperson (or designee) deems it appropriate to continue subject research participation during a lapse in approval, he/she will grant approval for continuance.

To assist the IRB Chairperson (or designee) with his/her determination, the Principal Investigator should provide the IRB Chairperson (or designee) with correspondence that should contain the following information:

- (i) a brief description of the study,
- (ii) a description of the specific study activity(ies) the PI wishes to continue until IRB approval is reinstated including discussion of why continuation is in the individual subjects' best interest,
- (iii) a listing by study number of each current subject for whom continued research participation is being requested,

- (iv) a description of the effect of the study activities described in #2 above regarding risks and benefits to subjects,
- (v) an explanation of why the PI failed to timely complete all information necessary for the IRB to perform a continuing protocol review and an explanation of what steps the PI is taking to assure a lapse does not occur in the future.

Additional guidance can also be found at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm115834.htm> and <http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.pdf>.

- t. **Suspension or Termination of IRB Approval.** All investigators conducting research at THR or as employees or agents of THR or in which THR is engaged are required to notify the IRB promptly of any unanticipated problems involving risks to subjects or others (refer to Section I of this Chapter for details.)

In addition, all employees and agents of THR or in which THR is engaged are required to notify the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or with the determinations of the IRB.

Continuing Non-compliance: Noncompliance (serious or non-serious) that has been previously reported, or a pattern of ongoing activities that indicate a lack of understanding of human subjects protection requirements that may affect research participants or the validity of the research and suggest the potential for future noncompliance without intervention.

Serious Non-compliance is defined by the THR to be failure to comply with laws or regulations, THR policies, or the requirements or determinations of the IRB when that failure actually or potentially increases risk to subjects adversely affects the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study. Willful violation of policies, state and local laws, and/or federal regulations may also constitute serious noncompliance. A single instance of non-compliance may be determined by the IRB to be serious non-compliance.

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. The IRB will notify the PI in writing of such suspensions or terminations and will include a statement of the reasons for the IRB's actions. The PI will be provided with an opportunity to respond.

Where the IRB Chairperson determines that such action is necessary to protect the rights and welfare of subjects, the Chairperson may require an immediate, temporary suspension of enrollment of new subjects or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

u. Notification to Texas Health Resources Officials Regarding IRB Findings.

The IRB Chair, in consultation with the Research Compliance Officer, must make a written report to THR officials when the IRB has made any of the following determinations:

- (i) Demonstrated unanticipated problems involving risk to human subjects or others.
- (ii) Suspension or termination of a previous approval to conduct research and/or activities associated with research
- (iii) Instances of serious or continuing non-compliance by a research site with regulations or IRB requirements.

Within 5 working days of the IRB determination, the IRB Chair (or designee) should send written notification to the following officials:

- THR Institutional Official
- THR Legal Counsel
- THR Chief Compliance Officer
- Principal Investigator

The notice can be made via email.

- (i) The written notice should include the following information:
 - Title of the research (include sponsor, protocol number, drug or device, if applicable)
 - Name of the Principal Investigator
 - IRB protocol number, and when applicable, grant number
 - The site(s) at which the research is being conducted

 - A detailed description of the problem, risk, or non-compliance issue(s) prompting the report
 - An explanation of the basis for determination that the issues or events are reportable
 - What corrective action is being taken or was taken
 - If the corrective action is complete, the initial report should provide details of corrective actions taken.
 - If the corrective action is incomplete or further action is forthcoming, details of corrective actions taken to date will

be included and a statement will be included in the report to explain that a final report will be provided upon implementation of the remaining corrective actions. A target date for completion should be included.

- Whether a suspension/termination is permanent or conditional, if applicable
- What additional actions, if any must be taken prior to resuming the research. For example, the IO may determine that further investigation is warranted.
- The notice will indicate (by carbon copy designation) others who are also being provided a copy of the notice
- The Research Compliance Office will maintain copies of all written notices.

v. External Reporting to Regulatory Agencies Regarding IRB Findings.

The THR Board of Trustees has designated an Institutional Official who is responsible for the submission of reports to regulatory agencies when required. In cases where the IRB and Institutional Official determine that additional information is needed before submitting a final report to a regulatory agency, a preliminary report should be submitted to the regulatory agency within 30 days of the IRB determination. Examples of agencies include the Office of Human Research Protection (OHRP) and Federal Drug Administration (FDA).

The following process should be followed:

- (i) The IO (in consultation with THR Legal Counsel and the THR Chief Compliance Officer) should review the IRB Chair's report within 5 working days from receipt to determine if a report must be filed with one or more regulatory agencies.
 - (a) If external reporting is deemed necessary, the IO (or designee) will draft a report for submission to the regulatory agency.
 - (b) If external reporting is not required, the IO (or designee) will communicate the determination to the IRB Chair and Research Compliance Officer.
- (ii) Any report to a regulatory agency will include the following information, at minimum:
 - The name of the institution conducting the research
 - Title of the research (include sponsor, protocol number, drug or device, if applicable)
 - Name of the Principal Investigator
 - IRB protocol number, and when applicable, grant number
 - The site(s) at which the research is being conducted

- A detailed description of the problem, risk or non-compliance issue(s) prompting the report
 - An explanation of the basis for determination that the issues or events are reportable
 - What corrective action is being taken or was taken
 - If the corrective action is complete, details should be included in the report
 - If the corrective action is incomplete or further action is forthcoming, details of corrective actions taken to date should be included and a statement should be included in the report to explain that a final report will be provided upon implementation of the remaining corrective actions. A target date for completion should be included.
 - If applicable, whether a suspension/termination is permanent or conditional
 - If applicable, what additional actions must be done to resume the research
- (iii) The final report is then submitted by the Institutional Official (or designee) to the appropriate parties:
- OHRP (for research covered by an OHRP-approved assurance).
 - Food and Drug Administration (for research subject to FDA regulation): Notification to the FDA may be made by either the IO or the study sponsor. If the study sponsor has been designated to make the report to the FDA, the IO must receive a copy of the study sponsor's report in order to confirm that the sponsor's report complies with this policy and with regulatory requirements.
 - Study Sponsor (if the research is industry-sponsored),
 - Any other agency with jurisdiction over the research study (if that agency requires reporting separate from reporting to OHRP, FDA, etc.)

Internal Recipients:

- THR Legal Counsel
- THR Chief Compliance Officer
- Research Compliance Officer
- IRB Chair (for inclusion in the next IRB meeting agenda)
- Principal Investigator

Additional Internal Recipients (when appropriate):

- Director of Clinical Research
- Principal Investigator's department chair.

- Other parties as identified by the IO
- (iv) If additional facts become apparent after the submission of the final report to a regulatory agency, the IO will complete an amendment to report any additional information or clarifications and submit the amendment to the previous agencies and internal parties who received the prior report(s).

Chapter 10. Criteria for IRB Approval of Research

Federal regulations at [45 CFR 46.111](#), FDA regulations at [21 CFR 56.111](#), and the Federal Policy (Common Rule at Section 111) delineate specific criteria for the approval of research. The IRB will determine that all of the following requirements are satisfied before approving proposed research.

- a. Levels of Risk.** The IRB must consider the overall level of risk to subjects in evaluating proposed research. In general, the regulations require that the IRB distinguish research that is “greater than minimal risk “ from research that is “no greater than minimal risk.” Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under Federal regulations at [45 CFR 46.102\(i\)](#), “minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

- b. Risks Minimized.** In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures already being performed on the subjects for diagnostic or treatment purposes.

The IRB is expected to consider the research plan, including the research design and methodology, to determine that there are no flaws that would place subjects at unnecessary risk. When the research design presents unnecessary or unacceptable risks to subjects without commensurate benefits to the subjects or to others, the research cannot ethically proceed.

In order to ascertain whether the research project is adequately designed and thus subjects protected, the IRB reserves the authority to seek opinions from consultants on proposed research and its design. The IRB may determine that proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, etc.

The IRB will also consider the qualifications of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Overall, the research team must possess the professional and educational qualifications to conduct the research project and to protect the

rights and welfare of subjects. In addition, the research team must possess the resources to conduct the research project and to protect the rights and welfare of subjects, which includes that there is adequate time for the researchers to conduct and complete the research, adequate number of qualified staff, adequate facilities and access to a population that will allow recruitment of the necessary number of participants.

- c. Risks Reasonable Relative to Anticipated Benefits.** In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and/or the importance of the knowledge that may reasonably be expected to result.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB should consider only those risks that result from the research, and should not consider long range effects (e.g., public policy implications) of applying the knowledge gained in the research.

- d. Equitable Selection of Subjects.** In order to approve research, the IRB must determine that the selection of subjects is equitable. In making this determination, the IRB should evaluate the purposes of the research and the research setting, and should be especially cognizant of the problems of research involving vulnerable subject populations, which include children, pregnant women, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB should carefully examine inclusion-exclusion criteria and recruitment procedures in order to determine that the burdens and benefits of the research are being distributed equitably.

Inclusion of Women and Minorities. It is the policy of THR that women and members of minority groups and their sub-populations must be included in all biomedical and behavioral research projects involving human subjects, unless a clear and compelling scientific rationale and justification is provided that inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

The IRB should be mindful of the desirability of including both women and men as research subjects and should not arbitrarily exclude the participation of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

Inclusion of Children. In June 1996, the American Academy of Pediatrics and the NIH held a joint workshop concerning the participation of children

in clinical research. There is valid concern that treatment modalities developed based on research conducted on adults, without adequate data from children, are being used to treat children for many diseases or disorders. Participants in the workshop concluded that there is a sound scientific rationale for including children in research, and investigators should be expected to do so unless a strong overriding justification can be offered to exclude them from studies. Investigators are encouraged to consider including children in clinical research studies.

THR investigators, and especially NIH-supported investigators, must provide details of the proposed involvement of humans in research, including the characteristics of the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review numbers are not included in the background data for a protocol, the investigators must provide a clear rationale for exclusion of this information. For additional information, refer to Section 492B of the Public Health Service Act, and [NIH Guide for Grants and Contracts, Vol. 23, Number 11, March 18, 1994](#).

- e. Informed Consent Procedures.** In order to approve research, the IRB must determine that legally effective informed consent will be sought from each prospective subject or the subject's legally authorized representative (see [45 CFR 46.116](#)), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver must be consistent with applicable laws. The specific elements required for legally effective informed consent are discussed in detail in [Chapter 12](#).
- (i) Informed consent may only be sought under circumstances that provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
 - (ii) Informed consent information must be presented in language that is understandable to the subject (or the legally authorized representative).
 - (iii) No informed consent process may include any exculpatory language (i) through which the subject is made to waive, or appear to waive, any legal rights as research subjects; or (ii) through which the investigator, the sponsor, THR, or THR's employees or agents are released from liability for negligence, or appear to be so released. For instance, it is appropriate for the consent document to state that certain specimens may be used for research purposes. However, using the word "donation" to characterize the future use of specimens

for research purposes implies abandonment of rights to the “property” donated. Whether or not the wording is contained in “the actual informed consent document” is immaterial. All study-related documents must be submitted to the IRB for review. Any separate “donation” agreement for future research use of specimens is regarded to be part of the informed consent documentation and must be in compliance with regulatory requirements.

- (iv) The subject must sign the informed consent document prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research. If the subject is determined eligible for the study during the pre-screening process and the subject has had all his/her questions answered about the study that are not regarding clinical issues and/or medical treatment, non-investigational clinical screening procedures for the study, e.g. blood work, may be performed after the subject signs the research consent form and before signature by the physician investigator (See Chapter 10, section f, items 1 and 2 for additional details on the consenting process.)
- (v) Alternatives to obtaining informed consent from the subject immediately before the start of the research include: (a) prior written consent from the subject, (b) surrogate consent from a legally authorized representative, (c) durable power of attorney, and (d) proxy. Alternatives (a) and (b) are taken from the regulations and are appropriate. Alternatives (c) and (d) allow a designated individual to provide informed consent for a patient with regard to health care decisions. When these alternatives are considered, the IRB must determine that applicable State law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions to be made on their behalf by others. These instances will be handled on a case-by-case basis.

f. Documentation of Informed Consent. In order to approve research, the IRB must determine that informed consent will be appropriately documented, unless documentation can be waived under Federal regulations (see the above section e, (iv) for additional information). Unless authorized by the THR IRB, all studies involving documentation of informed consent and reviewed by the THR IRB must use the applicable THR IRB informed consent form template(s), if available.

1) Studies that involve the practice of medicine, e.g. clinical testing, treatments, study device use or drug administration

In Texas, the duty of obtaining informed consent for medical treatment (the practice of medicine) is imposed solely upon the treating physician. Accordingly, it is a physician investigator’s non-delegable duty to obtain a subject’s consent for studies involving medical or surgical risks. However, upon the physician investigator’s request, a

research coordinator for the study may review, with the proposed subject, the study process and the research consent form. The study subject will be given the opportunity to ask questions regarding the study process including the alternatives, risks, and benefits of taking part in the study.

- a) If the subject has questions concerning clinical issues and/or medical treatment (the practice of medicine), the process will stop and the subject will be given the opportunity to meet with the physician investigator prior to the start of any study procedures including any screening.
 - i. The physician investigator will then discuss the study with the subject and address any of the subject's questions and document the discussion with the subject in the clinical record. The physician investigator will obtain the study subject's signature on the research consent form. He/She will also sign the research consent form himself/herself, attesting to the fact that the physician investigator reviewed the study's purpose, its experimental and non-experimental procedures and interventions, the possible risks and benefits, the standard and research aspects of the study, the alternatives to participation, the voluntary nature of participation, the HIPAA Privacy Rule, the source of funding for the research, conflict of interest on the part of the research staff, if any and answered all of his/her questions.
- b) If the subject has no questions pertaining to clinical issues and/or issues related to medical treatment (the practice of medicine), the research coordinator may obtain the subject's signature on the research consent form, and the research coordinator will sign as having reviewed the research consent form with the subject and having witnessed his/her signature.
 - i. The study subject may then begin screening procedures.
 - ii. Prior to the subject participating in any investigational procedures involving medical treatment, the physician investigator will ask the subject whether he/she has any questions regarding the study and document the discussion in the clinical record. The physician investigator will sign the research consent form attesting to the fact that the physician investigator reviewed the study's purpose, its experimental and non-experimental procedures and interventions, the possible risks and benefits, the standard and research aspects of the study, the alternatives to participation, the voluntary nature of participation, the HIPAA Privacy Rule, the source of funding for the research, conflict of interest on the part of the research staff, if any and answered all of his/her questions.

2) **Studies that do not involve initiation or alteration of medical treatment (the practice of medicine).**

A non-physician investigator, that is functioning within the scope of practice, may discuss the study procedures, alternatives, risks and benefits with the study subject, answer the questions of the study subject, obtain the signature of the study subject on the Informed Consent document and sign the document him/herself attesting to the fact that he/she has completed the informed consent process. The investigator, or approved study personnel, will document the process in the clinical record and/or research records, as applicable.

3) The IRB may determine that additional informed consent precautions must be taken.

4) **Long Form vs Short Form Documentation.** Federal regulations at [45 CFR 46.117](#) and [21 CFR 50.27](#) provide two methods for documenting informed consent:

- (i) Consent may be documented through use of a written consent document that embodies all of the required elements of informed consent (these elements will be discussed in detail in [Chapter 12](#)). The consent document must be signed and dated by the subject (or the subject's legally authorized representative), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated; and
- (ii) Consent may also be documented through use of a short form consent document which states that the elements of informed consent have been presented orally to the subject (or the legally authorized representative). When this method is used, (1) there must be a witness to the oral presentation who is conversant in both English and the language of the participant; (2) the IRB must approve a written summary that embodies the basic and required additional elements of disclosure of what is to be presented orally; (3) only the short form must be signed and dated by the subject or the representative; (4) the witness must sign both the short form and the summary; (5) the person actually obtaining consent must sign and date the summary; and (6) a copy of the summary and the short form will be given to the subject or the representative.

Date Stamp Required. All informed consent documents will have a date stamp with information regarding its approval by the IRB and that the use of the informed consent document will be valid only through a certain date.

The consent form will be stamped with the date of the meeting or date of study final approval, for expedited reviews, in which the protocol was approved (approved or approved with changes). Only the IRB-approved informed consent document can be used for the informed consent process. The investigator is responsible for keeping the signed, original informed consent documents, unless the THR Entity instructs the investigator to place it into the subject's medical record. In this case, the investigator would file a signed copy of the informed consent in his/her research office.

- g. Data Safety Monitoring.** In order to approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision for monitoring the data to protect the safety of subjects. For research in which risks are substantial, a general description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting unanticipated problems.

In general, it is desirable for a DSMB to be established for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions. 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, the IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, 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.

- h. Privacy of Subjects and Confidentiality of Data.** In order to approve research, the IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and the confidentiality of data.

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

- i. Additional Safeguards for Vulnerable Subjects.** In order to approve research, the IRB must determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as

children, prisoners, pregnant women, persons with mental disabilities, or economically or educationally disadvantaged persons.

Should THR's designated IRB find that they regularly review research involving such vulnerable subjects, the IRB will include among its reviewers persons who are knowledgeable about and experienced in working with these vulnerable subjects.

The IRB Chair, or designee, evaluates each protocol and ensures that at least one IRB member knowledgeable about or experienced in working with such subjects will be present at the meeting. The IRB Chair, or designee, will defer to another meeting or IRB, or obtain consultation if there is not appropriate scientific or representational expertise.

- j. Review More Often Than Annually.** THR's designated IRB recognize that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually.

THR's designated IRB will consider the following factors in determining which studies require more frequent review:

- (i) The probability and magnitude of anticipated risks to subjects (refer to Chapter 17, Table-VI Risk Determination for Continuing Review);
- (ii) The likely medical condition of the proposed subjects;
- (iii) The overall qualifications of the Principal Investigator and other members of the research team;
- (iv) The specific experience of the Principal Investigator and other members of the research team in conducting similar research;
- (v) The nature and frequency of adverse events observed in similar research at this and other Institutions; and
- (vi) 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.

- k. Independent Verification From Sources Other than the Investigator That No Material Changes Have Occurred Since the Previous IRB Review.** THR's designated 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 have occurred during the IRB-designated approval period.

THR's designated IRB will consider the following factors in determining which studies require such independent verification:

- (i) The probability and magnitude of anticipated risks to subjects;

- (ii) The likely medical condition of the proposed subjects;
- (iii) The probable nature and frequency of changes that may ordinarily be expected in type of research proposed;
- (iv) Prior experience with the Principal Investigator and research team; and
- (v) Any other factors that the IRB deems relevant.

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.

- I. Consent Monitoring.** In considering the adequacy of informed consent procedures, the IRB may require special monitoring of the consent process by a designated consent monitor (who serves as an impartial observer) 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. The duration of the special monitoring of the consent process can be either for a set time period or for a set number of subject enrollments.

Consent monitoring may also be appropriate as a corrective action where the IRB has identified problems related to the consenting of research subjects associated with a particular investigator or a research project. The IRB may also require that investigators include a “waiting period” within the consent process, or employ devices such as audiovisual aids or tests of comprehension.

When consent monitoring has been deemed necessary, the IRB will notify the Principal Investigator via written communication. The notification will contain the following elements:

- Notification to the Principal Investigator of a need to have monitoring of the consent process,
- The justification or rationale for this decision, and
- Any other relevant details (duration of consent monitoring, waiting period, etc.)

The Principal Investigator will be directed to inform the IRB of all upcoming scheduled visits, which might reasonably include efforts to enroll new subjects into the study. The IRB will designate a consent monitor who will arrange to be present during the consent process. Prior to the monitoring process, the IRB will inform the consent monitor of any particular issues that warrant special monitoring of the consent process.

Following the completion of monitoring process, the consent monitor will provide a written report detailing observations. If the consent monitoring process is expected to take a longer period of time (over a month), the consent monitor can present their observations as a series of written reports rather than issuing a cumulative report. Dependent on the nature of the observations, the consent monitor may also issue an emergency report to IRB, if warranted.

The consent monitor's report (or reports) will be shared with the IRB, which will determine if the Principal Investigator's process is adequate or if a corrective action plan (CAP) is required. The Board's decisions will be communicated to the Principal Investigator through normal mechanisms.

m. Advertisements and Recruitment Incentives. The IRB will review advertisements and recruitment incentives associated with the research that they oversee. Advertisements and incentives are directly related to the informed consent process and must be consistent with prohibitions on coercion and undue influence.

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:

- (i) The name and address of the Clinical Investigator and/or research Institution.
- (ii) The condition under study and/or the purpose of the research.
- (iii) In summary form, the criteria that will be used to determine eligibility for the study.
- (iv) A brief list of participation benefits, if any.
- (v) The time or other commitment required of the subjects.
- (vi) The location of the research and the person or office to contact for further information.

Recruitment procedures should be designed so that informed consent is given freely and coercion or undue influences are avoided. In order to evaluate this, the IRB should know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

Direct advertising for research study subjects (i.e. advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study) shall be reviewed by the IRB. Direct advertising includes, but is not limited to: newspaper, radio, TV, bulletin boards, posters, flyers, e-mail postings and THR digital screens.

IRB review and approval of listings of clinical studies on the THR internet/intranet is not required. Internet/intranet listings will limit the

information provided to basic study information, such as: The title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the study site for further information. All approved study advertisements to be placed on the THR digital screens and those to be disseminated to THR employees via e-mail must be submitted to the Texas Health Research & Education Institute for placement onto the digital screen and e-mail dissemination.

- n. Obtaining Consent from Non-English Speakers.** Federal regulations at [45 CFR 46.116](#) and [21 CFR 50.20](#) require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative).

In accordance with these regulations, informed consent discussions must include a reliable translator/interpreter when the prospective subject does not understand the language of the person who is obtaining consent.

As indicated in Item (f) above, investigators may document informed consent in either of two ways:

- (i) A full-length informed consent document written in language understandable to the subject; or
- (ii) A "short-form" consent document in the language of the subject that states the general elements of informed consent.

THR will provide generic "short form" consent documents to investigators in languages typically encountered among subject populations. Investigators will be responsible for providing documents in languages not typically encountered.

If investigators use the "short form" to document informed consent, they must also provide subjects with (i) the full-length informed consent document in English, and (ii) interpreter who can take part in the oral informed consent discussion to ensure subject's understanding and who may serve as the witness. The "short form" consent document written in the subject's language must be signed and dated by the subject (or the subject's legally authorized representative) and the witness, who will be conversant in both English and the language of the subject. The full-length English consent document must be signed and dated by the witness and the person obtaining consent. The subject must be given copies of both the "short form" consent document and the English consent document.

Whether a full-length or a "short form" consent document is utilized, the IRB will require that appropriately translated documents be submitted to the IRB for review and approval prior to their use in enrolling subjects.

- o. Payments to Research Subjects.** The IRB will review any proposed payments to research subjects associated with the research that they oversee. Payments to research subjects may not be of such an amount as to result in coercion or undue influence on the subject's decision to participate. Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation.

- p. Compensation for Injury.** The IRB will provide subjects with accurate information about the availability or absence of compensation and/or treatment for injury occurring in the research that it reviews.

The IRB is mindful that "injury" may include physical injury, psychological harm, social harm, or harm to one's dignity, depending upon the nature of the research.

- q. Certificates of Confidentiality.** Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes.

In such situations, the IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA for audit purposes. Consequently, the IRB will require that these conditions for release be stated clearly and explicitly in the informed consent document.

Information concerning Certificates of Confidentiality can be obtained from any of the following websites:

- <http://www.nimh.nih.gov/research/confident.cfm>
- <http://www.niaaa.nih.gov/extramural/confidential.htm>
- <http://www.nida.nih.gov/funding/confidentialityfaq.html>
- <http://www.hrsa.gov/quality/certconf.htm>
- <http://www.cancer.gov/clinicaltrials/conducting/certificates-of-confidentiality>
- <http://www.nhlbi.nih.gov/funding/policies/certsinfo.htm>

- r. Indemnity and Liability Provisions.** Subjects in THR research may not be asked to waive, or appear to waive, any of their legal rights.
- s. Compliance with All Applicable Laws.** All human subject research conducted at THR or by THR's employees or agents or in which THR is engaged must comply with all applicable Federal, State, and local laws and regulations.
- t. Waiver or Alteration of Informed Consent Requirements: State or Local Public Benefit Programs.** Federal regulations at [45 CFR 46.116\(c\)](#) permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:
- (i) The activity constitutes a research or demonstration project that 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; *and*
 - (ii) The research could not practicably be carried out without the waiver or alteration.

When appropriate, these findings and their justifications will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

- u. Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research.** Federal regulations at [45 CFR 46.116\(d\)](#) permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:
- (i) The research involves no more than minimal risk to the subjects;
 - (ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - (iii) The research could not practically be carried out without the waiver or alteration; and

- (iv) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

When appropriate, these findings and their justifications will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

- v. Waiver of Documentation of Consent.** Federal regulations at DHHS/OHRP [45 CFR 46.117\(c\)](#) and FDA 21 CFR 56.109(c)(1) permit an IRB to waive the requirement to obtain written documentation of informed consent. In order to approve such a waiver, the IRB must find and document **either** of the following conditions:

- (i) (DHHS/OHRP) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- (ii) (DHHS/OHRP and FDA) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

When appropriate, these findings and their justifications will be clearly documented in IRB minutes or IRB study file if study is determined to be minimal risk when the IRB exercises this waiver provision.

- w. Study Funding/Costs.**

Texas Health entities may contract with researchers from time-to-time to provide hospital services the researcher requires in connection with a clinical study pursuant to a contract with a study sponsor where the study sponsor has designated the researcher as the payee for all study activities. If the study sponsor has established a contracted price for the specific hospital service (and the researcher is the designated payee under the contract), the hospital must contract with the researcher to provide the needed hospital services at a price that is no less than the price established by the sponsor in the contract. If the hospital determines the price established by the sponsor is not reasonable, the hospital should negotiate a fair market price with the researcher. In cases where the researcher is

the designated payee and the contract does not specify a separate/specific price for the hospital service(s) and/or the pricing between the researcher and the study sponsor is held confidential, pricing for purchased hospital service(s) must be at fair market value as determined by the Texas Health Research and Compliance Committee (RACC). For this purpose, The RACC will establish fair market value from time-to-time giving consideration to the following: 1) Texas Health contracted rates with managed care companies, 2) Texas Health pricing provided to uninsured patients who have ability to pay, 3) Texas Health pricing for hospital services negotiated directly with clinical trial sponsors for the same or similar service, and 4) other data that may be deemed appropriate in establishing fair market value for the requested hospital test or service. Charges for hospital services provided pursuant to a purchased service contract between the hospital and a researcher will be billed timely to the researcher and properly credited to hospital accounts when received. Standard of care services (i.e. services that are a covered benefit and properly payable by insurance companies or other payers) provided to research subjects will be billed to payers in accordance with normal billing practices and consistent with billing requirements for patients enrolled in a clinical research study.

THR must be a party to all contracts related to any human research conducted at any THR Entity or in which any THR employee is engaged. The contract may be written between the THR Entity and the sponsor or between the THR Entity, the sponsor and the Principal Investigator. No approved consent form will be released by the IRB until a signed contract has been fully executed. The THR research Entity, if not a party to the contract, will acknowledge all contracts. The THR research Entity will receive all revenue from the research study from the sponsor for those studies in which a THR employee is engaged in the study or in which the hospital related research revenue is 50% or greater. If the THR research Entity receives the revenue, the THR research Entity will disseminate revenue to the Principal Investigator as per the conditions detailed in the contract between the THR Entity and the Principal Investigator. For studies in which the Principal Investigator directly receives the revenue from the research study, the Principal Investigator will sign a Hospital Service Agreement to indicate was research related revenue will be paid to the THR research Entity on behalf of the THR Entity by the Investigator. All studies will be assessed a charge for indirect costs incurred by the Entity at a rate of 25% which will be payable to the THR research Entity.

If THR has not received study payment from Principal Investigator or Study Sponsor within 6 months from time of study subject receiving hospital treatment, the study will be placed on hold to new enrollment and the THR Chief Compliance Officer and the Entity President will be notified.

Chapter 11. Required Elements of Informed Consent

One overarching requirement of research involving human subjects is that investigators must obtain the legally effective informed consent of prospective subjects before they can be included in research. Research investigators are responsible for obtaining and documenting informed consent in accordance with Federal regulations ([45 CFR 46.116](#) and [46.117](#) and [21 CFR 50.25](#), [50.27](#) and [21 CFR 56.109](#)) and THR-specific policies.

Informed consent presumes two simultaneous concepts: informed decision making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits in order to reach an **informed decision** as to whether they will **voluntarily participate**.

For an effective informed consent process, DHHS regulations at [45 CFR 46.116\(a\)](#), the Common Rule, and FDA regulations at [21 CFR 50.25\(a\)](#) mandate the inclusion of eight basic informed consent elements. Six additional elements may be required, depending on the nature of the research ([45 CFR 46.116\(b\)](#) and [21 CFR 50.25\(b\)](#)). The elements of informed consent as outlined in these regulations shall not preempt any other Federal, State, or local regulation which requires additional information to be disclosed for informed consent to be legally effective. Also nothing in these regulations is intended to limit the authority of a physician to provide emergency care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

The Informed Consent Template(s), which can be accessed via the [THR IRB website](#), provide specific guidance on how these should be worded and ordered for each THR Institution. Unless authorized by the THR IRB, all studies involving documentation of informed consent and reviewed by the THR IRB must use the applicable THR IRB informed consent form template(s).

- a. Research Statement (required element #1).** Informed consent information must include the following:
 - (i) A statement that the study involves research;
 - (ii) An explanation of the purposes of the research;
 - (iii) An explanation of the expected duration of subjects' participation;
 - (iv) A description of what procedures will be followed; and
 - (v) Identification of any procedures that are experimental.

- b. Reasonably Foreseeable Risks or Discomforts (required element #2).** Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research.

- c. Reasonably Expected Benefits to Subjects or Others (required element #3).** Informed consent information must describe any benefits to subjects or to others which may reasonably be expected from the research. However, benefits must not be overstated as to create an undue influence on subjects.
- d. Appropriate Alternatives (required element #4).** Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives. It is not sufficient simply to state that “the doctor will discuss alternatives to participating.”
- e. Extent of Confidentiality (required element #5).** Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who otherwise would not be privy to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects’ private information or records.
- f. Compensation or Treatment for Injury (required element #6).** Informed consent information for research involving more than minimal risk must include explanations regarding:

 - (i) Whether any compensation is available if injury occurs;
 - (ii) Whether any medical treatments are available if injury occurs and whether there is a charge for such medical treatment; and
 - (iii) A description of any such compensation or treatments or where more information about them is available.
- g. Contact Information (required element #7).** Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:

 - (i) For answers to questions about the research. The Principal Investigator and other members of the research team are appropriate contacts for this information.
 - (ii) For answers to questions about subjects’ rights. Contact the IRB Office for this information.
 - (iii) In the event of a research-related injury. Depending upon the nature of the research, the research team, the emergency services department, the IRB Office, the THR Institutional Official, THR legal Counsel, or the THR Chief Compliance Officer may serve as appropriate contacts for this information. Any billing inquiries for

research-related questions should be directed to the THR Business Office.

h. Voluntary Participation Statement (required element #8). Informed consent information must contain clear statements of the following:

- (i) Participation in the research is “voluntary;”
- (ii) Refusal to participate will involve “no penalty or loss of benefits to which the subject is otherwise entitled;” and
- (iii) The subject may discontinue participation at any time “without penalty or loss of benefits to which the subject is otherwise entitled.”

The involvement/participation of a THR employee as a subject in a research study is voluntary and has the right to refuse to take part, right to drop out without any penalty or loss of benefits.

It is particularly important for subjects and prospective subjects to understand and have complete confidence that declining to participate in research will not jeopardize their care.

i. Additional Elements Where Appropriate. Where appropriate, the regulations require that one or more of the following six additional elements be included in the informed consent information.

Unforeseeable Risks to Subjects, Embryos, or Fetuses. Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that there may be risks that are not known or not foreseeable.

Investigator-Initiated Termination of Participation. There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject noncompliance with research, subject not benefiting from direct-benefit research). The informed consent information should specify these circumstances.

Additional Costs. If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information.

Early Withdrawal/Procedures for Termination. Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to

withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.

Significant New Findings. Subjects will be informed of any new knowledge or findings about the medication or test article and/or the condition under study that may affect the risks or benefits to subjects or subjects' willingness to continue in the research.

Approximate Number of Subjects. For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.

- j. Requirement for Consent by Authorized Personnel.** Informed consent may only be obtained by personnel authorized to do so by the IRB. The person who conducts the informed consent interview must be knowledgeable about the study and be able to answer questions. Informed consent information can be presented by any qualified person involved in conducting the study and is not limited to persons with MD's or PhD's. Every effort should be made to list on the informed consent document those personnel who may actually give the informed consent information to the potential subject. Thus, only a Principal Investigator, Co-/Sub-Investigator, or study coordinator who is listed on the informed consent document can obtain informed consent. In Texas, the duty of informed consent for studies involving medical or surgical risks is imposed solely upon the treating physician: it is the physician's non-delegable duty. See Chapter 10 (sections e and f) for specific information regarding the obtaining of informed consent.
- k. Copy to Subject.** Once the informed consent information has been presented, the informed consent document is given to the subject for further review. The subject may take the document home to discuss the matter with family, friends, and/or spouses. When the subject decides to enter the study, he or she signs and dates the informed consent document. The original informed consent document is maintained by the investigator and a copy will be given to the subject and/or their legal representative for their records. Refer to Chapter 10, section f for additionally related information.
- l. Witness Signature.** Where it deems warranted, the IRB may also require the signature of a witness who has been present during the entire consent interview and who can attest that the information in the consent form, any other written information as well as questions and answers to and from the subject or the subject's legally authorized representative were conveyed in the consent process. The witness also attests to the validity of the subject's

or legally authorized representative's signature and that the informed consent was freely given by the subject or the subject's legally authorized representative. In order to ensure impartiality, the witness should not be a family member of the potential subject, a potential subject's legally authorized representative and/or a member of the study staff.

m. Data Retention When Subject Withdraw.

The IRB and investigators follow the following issues regarding data retention when subjects withdraw from a clinical trial:

- When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
 - The investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). The IRB must approve the consent document.
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

Chapter 12. FDA-Regulated Research: Investigational Drugs, Devices, and Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS) that is responsible for implementing and enforcing the Federal Food, Drug, and Cosmetic Act to regulate the safety and efficacy of these products for human use.

The FDA regulates clinical investigations that are conducted on drugs, biologics, and devices. All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review.

Clinical trials involving an investigational drug, device, or biologic that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with both the FDA and the DHHS human subject regulations (including, of course, the Common Rule).

- a. FDA versus Common Rule and DHHS Requirements.** The human subject protection requirements found in FDA regulations and DHHS regulations are substantially the same as the Common Rule requirements. However, there are important differences:
- (i) FDA regulations contain no Assurance requirement;
 - (ii) Conditions for exemption, exception, and waiver of IRB review and Informed Consent requirements differ;
 - (iii) FDA regulations require specific determinations for the IRB review of device studies (see below);
 - (iv) FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule or DHHS regulations;
 - (v) DHHS regulations include specific additional protections for pregnant women, fetuses, and human neonates ([Subpart B](#)) and prisoners ([Subpart C](#)) that are not contained in the FDA requirements; and
 - (vi) FDA regulations define “human subject” and “clinical investigation (research)” differently.

- b. INDs and IDEs.** Applications are submitted to FDA for approval of research involving an investigational drug, device, or biologic as follows:

Investigational New Drug Application (IND). An IND is submitted so that an investigation can be conducted in support of a potential New Drug Application.

Investigational Device Exemption (IDE). An IDE supports research to be conducted for a Pre-Market Approval application. Devices that are

substantially equivalent to other devices that are legally on the market are called 510(k) devices and can be marketed without clinical testing (see item [“d”](#) below).

Biologics License Application. A Biologics License Application is submitted to the FDA to receive approval for research on biological products that would support a Biologics License. Biologics include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

Application Exemptions.

It is not necessary to submit an application to the FDA if the product(s) qualifies under one or more of the following exemption categories:

Exemption 1

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product.
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- The investigation is conducted in compliance with 21 CFR 50 and 56.
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

Exemption 2

- A clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following:
 - Blood grouping serum.
 - Reagent red blood cells.
 - Anti-human globulin.
- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The diagnostic test is shipped in compliance with 21 CFR 312.160.

Exemption 4

- A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
- 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).
- 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).
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

The device fulfills one of the IDE exemption categories:

- 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.
- 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 part 807 in determining substantial equivalence.
- A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - Is noninvasive.
 - Does not require an invasive sampling procedure that presents significant risk.
 - Does not by design or intention introduce energy into a subject.
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- 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.
- 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.

c. Investigator and Sponsor Responsibilities.

Basic Investigator Responsibilities. Under FDA regulations, the **investigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

- (i) obtaining IRB approval;
- (ii) complying fully with the regulations;
- (iii) supervising the use and disposition of the test article; and
- (iv) disclosing relevant financial information.

Basic Sponsor Responsibilities. The **Sponsor** of a clinical investigation initiates and holds the IND or IDE for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation.

- d. IRB Review of Medical Devices.** In accordance with FDA requirements, it is the policy of THR that a decision of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk vs Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

Significant Risk (SR) Device Defined. A SR device study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant, or (2) is used in supporting or sustaining human life, or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full Board approval.

Nonsignificant Risk (NSR) Device Defined. A NSR device study is one that does not meet the definition of a SR study.

Review Procedures. The following procedures govern IRB review of investigational devices.

- (i) If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a SR, then it would be governed by the IDE regulations at [21 CFR 812](#). The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:
 - A description of the device;
 - Reports of prior investigations conducted with the device;
 - The proposed investigational plan;
 - A description of subject selection criteria;

- Monitoring procedures; and
- The sponsor risk assessment and the rationale used to make the sponsor's risk determination;

The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment;

- (ii) A device study that is deemed to involve a NSR may begin immediately after appropriate IRB review and approval, since it would not require the submission of an application to the FDA; and
- (iii) It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.

510(k) Devices. The review requirements for 510(k) devices are somewhat different. If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations.

- e. **Radiology Devices and Radioactive Materials.** FDA is responsible for regulating radiology devices and radioactive materials used in health care and research. Local oversight in this area is managed by the THR Entity's designated Committee(s).
- f. **Adverse Events and Reporting Requirements – INDs.** FDA IND regulations require that the investigator report promptly to the Sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" ([21 CFR 312.64\(b\)](#)).
 - (i) FDA and DHHS regulations require prompt reporting to the IRB, FDA, and OHRP of any unanticipated problems involving risks to subjects or others.
 - (ii) FDA IND regulations require the clinical investigator to notify the sponsor of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.
 - (iii) THR requires that any unanticipated problem information submitted to the Sponsor also be submitted to the IRB. Appropriate notification will be made to relevant Federal regulatory bodies, including FDA and OHRP, of any unanticipated problems involving risks to subjects or others, and of the resolution of those events or problems. Refer to Chapter 9 for additional guidance.
 - (iv) FDA IND regulations require that the Sponsor notify the FDA and all participating investigators of any unanticipated problem associated with the use of the drug or biologic that is both serious and unexpected as soon as possible but in no event later than 15

calendar days after the sponsor determines it to be reportable. “Serious adverse drug experience” is defined as “any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect” ([21 CFR 312.32\(a\)](#)). The FDA should be notified by telephone, facsimile, or in writing as soon as possible but in no event later than 7 calendar days of the sponsor’s receipt of the information of any unexpected fatal or life-threatening experience.

Investigators’ Duty to Report.

Refer to Chapter 9 for guidance.

Reporting Requirement.

Refer to Chapter 9 for guidance.

- g. Adverse Events and Reporting Requirements – IDEs.** FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect within 10 days.
- (i) Appropriate notification will be made to relevant Federal regulatory bodies, including FDA and OHRP, of any unanticipated adverse device effects or unanticipated problems involving risks to subjects or others, and of the resolution of those events or problems.
 - (ii) The Sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to the IRB within 10 working days of the sponsor’s receipt of the information.
 - (iii) Since 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects must follow these same requirements.

Investigators’ Duty to Report.

Refer to Chapter 9 for guidance.

Reporting Requirement.

Refer to Chapter 9 for guidance.

- h. Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice Versus Research.** Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If

physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

- (i) Off-label use of a marketed product in this manner when the intent is solely the **practice of medicine** does not require IRB review or the submission of an IND or IDE.
- (ii) Off-label use of a marketed product in **research** (i.e., as part of a systematic investigation designed to develop or contribute to generalizable knowledge) does require IRB review.
- (iii) Off-label use of a marketed product intended to support **a change in labeling** requires both IRB review and submission of an IND or IDE.

Per 21 CFR 312.2(b)(1), a marketed drug or biologic does not require submission of an IND if the 6 conditions specified in the regulation are met.

- i. Treatment INDs and IDEs.** The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. Where necessary, this mechanism can be used even for providing such drugs to a single patient-subject. The Treatment IDE is a comparable mechanism for providing investigational devices to such patient-subjects.

The FDA regulations at [21 CFR 312.34](#) and [312.35](#) specify the requirements that must be satisfied before a Treatment IND can be issued. The FDA regulations at [21 CFR 812.36](#) specify the requirements that must be satisfied before a Treatment IDE can be issued.

Treatment IND and IDE studies require prospective IRB review and informed consent. Although the sponsor may apply for a waiver of local IRB review under a Treatment IND or IDE, such a waiver does not apply to the informed consent requirement. It is the policy of THR that all Treatment IND or IDE studies must be reviewed and prospectively approved by the IRB.

Treatment IND. During the clinical investigation of a drug, it may be appropriate to use the drug in treatment of patients not in the clinical trials. Such use requires FDA approval under a treatment protocol ([21 CFR 312.35](#)) or a treatment IND ([21 CFR 312.34](#)), as well as IRB review and approval and informed consent.

Single Patient Treatment IND. The Single-Patient Treatment IND is not described in regulations yet, but was added to the law under the FDA Modernization Act (FDAMA) in 1997. From an operational standpoint, the

Single-Patient IND must meet the same requirements as a standard IND, and requires IRB review and approval and informed consent.

Group C Treatment IND. Group C drugs are Phase 3 study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are distributed by the National Cancer Institute (NCI) with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, THR policy normally requires review and approval by the THR IRB. Investigators who are considering use of Group C drugs should contact the IRB Chairperson for guidance.

Orphan Drugs. The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of orphan drugs requires prospective IRB review and approval and informed consent ([21 CFR 316.40](#) and [312.34](#)).

Parallel Track Studies. FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent (57 FR 13250).

Treatment IDE. Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use may occur when: (i) the patient has a serious or immediate life-threatening condition; (ii) there is no comparable or satisfactory alternative available; (iii) the device is under investigation in a controlled trial for the same use (or such trials have been complete); (iv) the Sponsor is pursuing marketing approval/clearance; (v) the Sponsor has submitted and the FDA has approved an IDE under [21 CFR 812.36](#). Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required.

- j. Gene Transfer Research.** Gene transfer research involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by both the FDA and the NIH Office of Biotechnology Activities (OBA).
- (i) FDA regulations require the submission of an IND for human gene transfer research.
 - (ii) DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by

the Recombinant DNA Advisory Committee (RAC) at NIH; approval of relevant THR Entity-designated Committee(s) has been obtained; IRB approval has been obtained; and the investigator has obtained all other regulatory authorizations (such as any consents required by regulations) from the subject (65 FR 196, [October 10, 2000](#)).

- (iii) While the RAC is advisory to the Director of the National Institutes of Health (NIH), compliance with its guidelines is mandatory for all investigators at Institutions that receive NIH funds for research involving recombinant DNA.

k. Emergency Use of a Test Article without IRB Review. An exemption under FDA regulations at [21 CFR 56.104\(c\)](#) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per Institution without IRB review and approval.

The physicians/investigators may consult with the IRB Chairperson or designee for guidance when considering the emergency use of drugs or medical devices.

Required Conditions. All of the following conditions must be met for this type of emergency use:

- (i) A human subject is in a life-threatening situation;
- (ii) No standard acceptable treatment is available;
- (iii) There is insufficient time to obtain IRB approval;
- (iv) The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB; and
- (v) Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below:

Emergency Use of Drugs. Emergency use of an investigational new drug occurs when the emergency situation does not allow time for submission of an IND. Use of the drug requires a request to FDA to authorize shipment of the drug for the emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable ([21 CFR 312.36](#)). The emergency use of an investigational new drug may take place without IRB review and approval, provided that the use is reported to the IRB within 5 working days. Informed consent is required unless the situation is life-threatening, the criteria at [21 CFR 50.23\(a\)](#) or [50.23\(b\)](#) have been met, and the IRB is notified within 5 working days.

Emergency Use of Devices. Emergency use of an unapproved device may occur in an emergency situation when (i) an IDE for the device does not exist, (ii) a physician wants to use a device in a way not approved

under an existing IDE, or (iii) when a physician is not an investigator under the existing IDE. The device may be used if (i) the patient has a life-threatening condition that needs immediate treatment, (ii) there is no generally acceptable alternative treatment, and (iii) there is no time to obtain FDA approval (50 FR 42866 21 CFR 812.35(a)). Such uses require as many of the following patient protections as possible (FDA Center for Devices and Radiological Health Guidance on IDE Policies and Procedures, January 20, 1998): (i) informed consent; (ii) clearance from the Institution; (iii) concurrence of the IRB chairperson (this concurrence does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization from the IDE sponsor (if an IDE exists). Follow-up reports should be provided to the Sponsor if an IDE exists, or to FDA if no IDE exists. Such use is limited to a few patients.

- I. Emergency Use of a Test Article without Informed Consent.** An exception under FDA regulations at [21 CFR 50.23](#) 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 physicians/investigators may consult the IRB Chairperson or designee for guidance when considering the emergency use of drugs or medical devices.

Required Conditions. All of the following conditions must be met for this type of emergency use:

- (i) The subject is confronted by a life-threatening situation necessitating the use of the test article;
- (ii) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
- (iii) Time is not sufficient to obtain consent from the subject's legally authorized representative;
- (iv) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life;
- (v) If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within five working days; and
- (vi) The emergency use must be reported to the IRB within five working days. This reporting must not be construed as an approval for the emergency use by the IRB.

m. Compassionate Use of Investigational Drugs and Devices.

“Compassionate Use” is not a term that appears in the FDA or DHHS regulations or the Common Rule. For studies involving investigational drugs “Compassionate Use” is often meant to refer to the emergency use situations discussed above. For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition who does not qualify for the trial. Such uses require prior FDA approval of a protocol deviation under [21 CFR 812.35\(a\)](#). Prior FDA approval for compassionate use should be obtained before the device is used.

On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the following protections as possible: (i) informed consent; (ii) clearance from the Institution; (iii) concurrence of the IRB Chairperson (which does not constitute IRB approval; (iv) an independent assessment of an uninvolved physician; and (v) authorization of the IDE sponsor. Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients.

THR Requirements. Despite these provisions, THR policy generally requires informed consent and IRB review, even in “compassionate use” situations. Investigators must consult the IRB Chairperson for guidance when considering the use of “compassionate use” interventions.

NOTE: The above “Compassionate Use” situations should not be confused with the Humanitarian Use Device (HUD) Exemption (see item “n” below).

- n. Humanitarian Device Exemptions.** A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission of a humanitarian device exemption (HDE) application. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. The labeling for an HUD must state that the

device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

An approved HDE authorizes marketing of the HUD. However, a HUD may only be used after approval of the convened (full) IRB has been obtained for use of the device at the Institution for the FDA approved indication ([21 CFR 814.124\(a\)](#)). After granting initial approval, the IRB may use expedited procedures for conducting continuing review. Informed consent of patients is not required because an HDE provides for marketing approval, so use of the HUD does not constitute research.

The use of HUDs does not constitute research. Therefore, conflict of interest disclosures are not required for HUD submissions.

- o. Planned Emergency Research.** An exception under FDA regulations at [21 CFR 50.24](#) permits planned research in an emergency setting without the informed consent of the subjects.

Planned emergency research that is not FDA-regulated is also permitted by DHHS and the Common Rule when specific Department or Agency action is taken to exercise the waiver provision at [45 CFR 46.101\(i\)](#). However, planned emergency research is usually subject to FDA regulations because it usually involves use of an FDA-regulated test article. When this is the case, the FDA requirements govern, and no notification of OHRP is required.

It is the responsibility of the IRB Chairperson to provide prompt written notification to the THR Institutional Official should the IRB approve planned emergency research.

Required Conditions. Planned emergency use of a test article may be approved under FDA regulations at [21 CFR Part 50](#) as follows:

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 subject is the equivalent of a family relationship.

§ 50.24 Exception from informed consent requirements for emergency research.

- (a) The IRB responsible for the review, approval, and continuing review of the clinical investigation may approve that investigation without requiring that informed consent of all research subjects be obtained if the 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) finds and documents each of the following:

- (1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- (2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
- (3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) Subjects are facing a life-threatening situation that necessitates intervention; (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- (4) The clinical investigation could not practicably be carried out without the waiver.
- (5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with [21 CFR 50.25](#). These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved

procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) below.

- (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) 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; (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and (v) if obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
- (b) The IRB is responsible for implementing procedures to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also maintain procedures to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be

- provided to the subject's legally authorized representative or family member, if feasible.
- (c) The IRB determinations required by paragraph (a) above and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with [21 CFR 56.115\(b\)](#).
 - (d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are 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. Applications for investigations under this section may not be submitted as amendments under [21 CFR 312.30](#) or [812.35](#).
 - (e) If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) above or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor. [61 [FR](#) 51528, October 2, 1996]

Chapter 13. Social and Behavioral Research

Social and Behavioral Research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention.

- a. Social and Psychological Harms.** When evaluating social and behavioral science research, the IRB carefully examines the research to determine the probability of risk of harm to subjects.
- (i) The IRB considers the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
 - (ii) The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, reputation; stigmatization; and damage to social relationships.
 - (iii) Collecting any identifiable, private information about any living individual constitutes human subject research. If information is being collected on living individuals in addition to the primary “target” subjects, the IRB will consider the risk of harm to those “non-target” individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of “non-target” individuals (unless the requirement for informed consent can be waived).

In order to mitigate such harms, the IRB reviews proposed research for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.

- b. Privacy and Confidentiality Concerns.** The use of confidential information is an essential element of much Social and Behavioral Research.
- (i) It is important to be sure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individual. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements. These circumstances will be discussed briefly in the following sections of this chapter.

- (ii) It also is important to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects.

c. Safeguarding Confidentiality. When information linked to individuals will be recorded as part of the research design, the IRB requires that adequate precautions will be taken to safeguard the confidentiality of the information.

- (i) When reviewing survey and interview research, the IRB will be aware of the regulatory provision at [45 CFR 46.117\(c\)\(1\)](#) for waiving documentation of consent when a signed consent form would itself constitute a risk to the subjects.
- (ii) Among the available methods for safeguarding confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.
- (iii) Regulations at [45 CFR 46.116\(a\)\(5\)](#) and FDA regulations require that subjects be informed of the extent to which confidentiality of research records will be maintained (or not maintained).
- (iv) Federal officials have the right to inspect research records, including consent forms and individual medical records, to ascertain compliance with the rules and standards of their programs. FDA requires that information regarding this authority be included in the consent information for all research that it regulates. Identifiable information obtained by Federal officials during such inspections is subject to both the privacy provisions and the disclosure provisions of the Privacy Act of 1974.
- (v) The IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

Information concerning Certificates of Confidentiality can be obtained from any of the following websites:

<http://www.nimh.nih.gov/research/confident.cfm>
<http://www.niaaa.nih.gov/extramural/confidential.htm>
<http://www.nida.nih.gov/funding/confidentialityfaq.html>
<http://www.hrsa.gov/quality/certconf.htm>
<http://www.cancer.gov/clinicaltrials/conducting/certificates-of-confidentiality> <http://www.nhlbi.nih.gov/funding/policies/certsinfo.htm>

d. Exempt Research. Much Social and Behavioral Research is exempt from the requirements of the Federal regulations ([45 CFR 46.101\(b\)](#)). However, appropriate application of these exemptions requires a level of expertise

and is not left to individual investigators. In reviewing exemption requests, the IRB must elicit enough information from the investigator to ascertain whether the claimed exemption really applies.

All exemptions claimed for research conducted at THR, or by employees or agents of THR or in which any THR employee is engaged, must be verified by the Chairperson of the IRB, or such an individual as the Chairperson has designated. The exemptions do not apply to research involving prisoners. The exemptions do apply to research involving pregnant women, fetuses, and neonates. See [Chapter 8, Item \(i\)](#) for additional details.

The following exemptions are particularly applicable to Social and Behavioral Research.

- (i) Research in Educational Settings;
- (ii) Research Using Educational Tests (Cognitive, Diagnostic Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or The Observation of Public Behavior; and
- (iii) Research using Existing Materials.

- e. Expedited Review of Social and Behavioral Research.** Social and Behavioral Research that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998 Federal Register. Click on the following link to access those categories: [Expedited Categories](#).

However, these categories do NOT apply to research involving prisoners.

The categories discussed below are particularly applicable to Social and Behavioral research, and include research involving children as well as adult subjects. See [Chapter 9 Item \(g\)](#) for additional details.

- (i) Research Involving Existing Materials;
- (ii) Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes; and
- (iii) Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies.

- f. Research Involving Deception.** Deception research involves social science research in which the subject is not told, or is misled, about the true purpose of the research, such as in certain studies of group processes, contextual influences on cognition, etc. IRBs reviewing research involving

incomplete disclosure or outright deception must apply both common sense and sensitivity to the review.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects will be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a countervailing benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that waiver of the usual informed consent requirements is justified under the criteria present at [45 CFR 46.116\(d\)](#). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

- (i) The research presents no more than minimal risk to subjects;
- (ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (iii) The research could not practicably be carried out without the waiver or alteration; and
- (iv) Where appropriate, the subjects will be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB will consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. Note that the regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects.

Chapter 14. Large Sample, Genetic, and Family History Research

- a. Research Utilizing Large Existing Data Sets.** Both Biomedical Research and Social and Behavioral Research often involve the use of large, existing data sets.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information (see item "[b](#)" above). Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of large, existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

- (i) In making this determination, the IRB will first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.
 - (ii) If this is not the case, then the IRB will consider whether it is permissible to waive the usual informed consent requirements in accordance with [45 CFR 46.116\(d\)](#). Many times, a waiver of consent will be appropriate.
 - (iii) In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities.
 - (iv) An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by OHRP (see below and refer to Guidance on this topic on the OHRP Website).
- b. Research Utilizing Data or Tissue Repositories.** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

Repository activities involve three components: (i) the **collectors** of data or tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators.

Under a repository arrangement, an IRB formally oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is not required. (Refer to Guidance on this topic on the OHRP Website.)

Typically, these parameters involve formal, written agreements stipulating these conditions:

- (i) The repository will not release any identifiers to the investigator;
- (ii) The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects;
- (iii) The investigator will use the data only for the purposes and research specified; and
- (iv) The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

c. Epidemiology Research. Epidemiology research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiology research may also combine historical research with survey and interview research.

Epidemiology studies often present significant problems regarding both **privacy** and **confidentiality**.

- (i) The IRB will first consider privacy issues, and must be satisfied that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB will seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.
- (ii) Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB will seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

- (iii) Because epidemiology research typically requires very large numbers of subjects, epidemiology investigators almost always request that the IRB waive the usual requirements for informed consent. In order to approve such a waiver in epidemiology research, the IRB must find and document that the first three criteria at [45 CFR 46.116\(d\)](#) for a waiver of informed consent have been met; specifically that (a) the research presents no more than minimal risk to subjects; (b) the waiver will not adversely affect the rights and welfare of the subjects; and (c) the research could not practicably be carried out without the waiver. The fourth requirement (“whenever appropriate, the subjects will be provided with additional pertinent information after participation”) usually does not apply.

d. Issues in Genetic Research. Information obtained through genetic research may have serious repercussions for the subject or the subject’s family members. Genetic information can adversely affect an individual’s insurability and employability.

The IRB needs to be particularly careful about approving research that appears to involve only a simple, minimal risk blood draw, but then goes on to include or add a component involving genetic analysis. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

e. Family History Research. Family history research is a common technique used in Bio-Social and Bio-Behavioral Research. Family history research typically involves obtaining information from one family member (called a proband) about other family members.

- (i) It is important to recognize the Federal regulations and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains “identifiable private information.”
- (ii) Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.
- (iii) The IRB must determine whether family members are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at [45 CFR 46.116\(d\)](#).

Chapter 15. Potentially Vulnerable Subject Groups

DHHS regulations at [45 CFR 46.111\(b\)](#), FDA regulation at [21 CFR 56.111\(b\)](#), and the Common Rule require IRBs to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB is required to include adequate representation on the Board to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

a. Elements to Consider. The IRB pays special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.

- (i) Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and voluntarism; coercion and undue influence; and confidentiality of data.
- (ii) The IRB will carefully consider group characteristics, such as economic, social, physical, and environmental conditions, so that the research incorporates additional safeguards for vulnerable subjects.
- (iii) Investigators will not generally be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available “captive” population.
- (iv) As it determines necessary, the IRB will seek to obtain information regarding laws and science that bear on decision-making capacity of the potentially vulnerable populations to be involved in the research.
- (v) Just as in providing medical care, research studies that involve potentially vulnerable populations must have adequate procedures in place for assessing subjects’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB will look to see that such procedures are a part of the research plan.
- (vi) In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include the inclusion of a consent monitor, a subject advocate, interpreter

for hearing-impaired subjects, translation of informed consent documents into languages the subjects understand, and reading the consent form to subjects slowly to gauge their understanding paragraph by paragraph.

- (vii) The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent documents to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.
- (viii) The IRB determines that research studies have the necessary resources to protect subjects, including the availability of medical or psychosocial resources that subjects may need as a consequence of the research.

b. Pregnant Women, Human Fetuses and Neonates. DHHS regulations at [45 CFR Part 46, Subpart B](#) detail special protections for research involving pregnant women, human fetuses, and neonates. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. In general, [Subpart B](#) requires that research involving pregnant women and fetuses should involve the least possible risk.

On the other hand, unilateral exclusion of non-pregnant women of reproductive potential from research, in order to avoid a risk, should not be permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Four separate categories, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses and neonates, as outlined below. IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category should be clearly documented in IRB records. DHHS Regulations at 45 CFR Part 46 provide the following in pertinent part.

Pregnant Women and Fetuses Prior to Delivery.

§ 46.204 Research involving pregnant women or fetuses prior to delivery.

Pregnant women or fetuses prior to delivery may be involved in research if all of the following conditions are met:

- (a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
- (b) The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by

interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) The woman's consent or the consent of her legally authorized representative is obtained in accord with the informed consent provisions of subpart A of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d);

(e) The woman or her legally authorized representative, as appropriate, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child;

(f) For children as defined in [45 CFR 46.402\(a\)](#) who are pregnant, assent and permission are obtained in accord, with the provisions of [subpart D](#) of this part;

(g) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(h) 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

(i) Individuals engaged in the research will have no part in determining the viability of a fetus.

Fetuses After Delivery.

§ 46.205 Research involving fetuses after delivery.

(a) After delivery, fetuses 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 fetuses.

(2) The individual(s) providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child.

(3) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

(4) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

(5) Individuals engaged in the research will have no part in determining the viability of a fetus.

(6) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Fetuses of uncertain viability. After delivery, and until it has been ascertained whether or not a fetus is viable, a fetus may not be involved in research covered by this subpart unless the following additional conditions are met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the particular fetus to the point of viability, and any risk is the least possible for achieving the objectives of the research, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the fetus resulting from the research; and

(2) The legally effective informed consent of either parent of the fetus 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 subpart A of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d).

(c) Nonviable fetuses. After delivery, a nonviable fetus may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the fetus will not be artificially maintained;

(2) The research will not terminate the heartbeat or the respiration of the fetus;

(3) There will be no risk to the fetus 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 fetus is obtained in accord with [subpart A](#) of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable fetus will suffice to meet the requirements of this paragraph. The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice to meet the requirements of this paragraph.

(d) Viable fetuses. A fetus, after delivery, that has been determined to be viable is a child as defined by §46.402(a) and may be included in research only to the extent permitted by and in accord with the requirements of [subparts A](#) and [D](#) of this part.

Placenta, Dead Fetus, or Fetal Material After Delivery.

§ 46.206 Research involving, after delivery, the placenta, the dead fetus, or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of 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 subparts of this part are applicable.

Other Research Affecting Pregnant Women or Fetuses.

§ 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 only if:

(a) 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 or fetuses; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable, or

(2) The following:

(i) 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 or fetuses;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of [subpart A](#) and other applicable subparts of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d).

[66 [FR](#) 20589, April 24, 2001].

- c. **Research Involving Prisoners.** DHHS regulations at [45 CFR Part 46, Subpart C](#) detail special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research.

Note that the THR IRB is neither constituted nor approved by DHHS/OHRP to review studies with prisoners.

- (i) A prisoner is defined as any individual involuntarily confined or detained in a penal institution.
- (ii) In order to consider research involving prisoners, the IRB must:
 - (a) Have a majority of its members not otherwise associated with the prison; and
 - (b) Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.
- (iii) The IRB that approves research involving prisoners must:
 - (a) Make the seven additional findings set forth in [45 CFR 46.305](#) that are listed below in Item (v);
 - (b) Determine which category in [45 CFR 46.306](#) permits the research to go forward; and
 - (c) If the research is DHHS-supported, certify these findings to OHRP. Certification to OHRP is not required for research not supported by DHHS. However, THR recommends that the IRB apply the standards of [Subpart C](#) to all prisoner research. Should non-DHHS research fall outside the category stipulations under [45 CFR 46.306](#), THR recommends that the IRB consult with appropriate experts before approving the research.
- (iv) Under DHHS regulations, prisoners may participate in the following categories of research:
 - (a) Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior;
 - (b) Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons;
 - (c) Research on particular conditions affecting prisoners as a class (providing the Secretary of DHHS has consulted with appropriate experts and published the intent to support such research in the Federal Register); and
 - (d) Research involving practices that have the intent and reasonable probability of benefiting the prisoner subject. If the research involves possible assignment to a control group that may not benefit from the research, the Secretary of DHHS must also consult with appropriate experts and publish the intent to support the research in the Federal Register ([45 CFR 46.306](#)).
- (v) The following additional determinations must be made by the IRB before research involving prisoners goes forward ([45 CFR 46.305](#)):
 - (a) The research under review is limited to one of the categories of research listed above;
 - (b) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared with 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;

- (c) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
- (d) Procedures for selecting 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;
- (e) The information is presented in language that is understandable to the subject population;
- (f) Adequate assurance exists that parole boards 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
- (g) Where the board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoner's sentences, and for informing participants of this fact.

- d. Research Involving Children.** DHHS regulations at [45 CFR Part 46, Subpart D](#) and FDA Regulations at [21 CFR 50 Subpart D](#) require special protections for research involving children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted. THR has determined that this age is 18 years in the State of Texas.

There are several important issues for the IRB to consider when reviewing research involving children, particularly including: (i) the risk-benefit analysis; (ii) permitted regulatory categories; (iii) parental permission; and (iv) assent of the child.

Risk-Benefit Analysis. The IRB must make certain specific findings and determinations when reviewing research involving children. IRB records must reflect the IRB's understanding and justification for the risks and benefits posed by approved research involving children.

Permitted Categories. Based in part on its risk-benefit analysis, the IRB must find and document that the proposed research falls within one of the following four categories:

- (a) Research not involving greater than minimal risk;
- (b) Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects;
- (c) 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; and
- (d) Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Each category stipulates specific conditions that must be met before the proposed research can be approved. These conditions are summarized in the Table on the next page.

Parental Permission. The IRB must determine that adequate provisions are made for obtaining and documenting parental permission for the child's participation in the research. Depending upon the category in which the research falls (see above), the permission of one or both parents may be required as a condition of the child's participation.

Assent of the Child. The IRB must also determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining when children are capable of assenting, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.

Wards of the State and Research Setting. The IRB determines whether the criteria for approval of research are met and documents when the research: is:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

Child Advocate. The IRB requires appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of

the child as guardian or *in loco parentis*.

- The advocate is an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research
- The advocate 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.

Table 15-1. Category Requirements for Permissible Research Involving Children.

Regulatory Category	Requirements
No Greater Than Minimal Risk	<ul style="list-style-type: none"> • Assent of child and permission of at least one parent
Greater Than Minimal Risk and Prospect of Direct Benefit	<ul style="list-style-type: none"> • Assent of child and permission of at least one parent • Anticipated benefit justifies the risk • Anticipated benefit is at least as favorable as that of alternative approaches
Greater Than Minimal Risk and No Prospect of Direct Benefit	<ul style="list-style-type: none"> • Assent of child and permission of both parents • Only a minor increase over minimal risk • Likely to yield generalizable knowledge about the child’s disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition • The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child’s actual or expected medical, dental, or expected medical, dental, psychological, social, or educational situations
Other Research	<ul style="list-style-type: none"> • Assent of child and permission of both parents • IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children • The DHHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following public comment

When Assent is Not Required. The assent of the child is not a necessary condition for the research if the IRB determines that:

- (i) The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- (ii) 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.

Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement where (i) the research involves no more than minimal risk; (ii) the waiver will not adversely affect subjects' rights and welfare; (iii) the research could not practicably be carried out without the waiver; and (iv) when appropriate, the subjects will be provided with pertinent information after participation.

Reasonable Expectation of Benefit. The IRB should take great care in approving research where the child is suffering from a life-threatening illness with little real chance of therapeutic benefit from the research. The IRB should also take great care in allowing the parents to overrule the child's dissent where experimental therapy has little or no reasonable expectation of benefit.

Documentation of Assent. If it is deemed appropriate that the child's assent should be solicited, the assent form should be tailored for the child, with respect to his or her level of understanding. For young children, the assent form should be a relatively brief document, with simple, age-appropriate language, presented in a manner understandable to the child.

- e. Research Involving Decisionally Impaired Subjects.** Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decisionally impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

In cases where research involving cognitively impaired individuals is approved, the IRB should consider additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

- f. Research Involving Potentially Addictive Substances.** Research involving potentially addictive substances often involves the use of what may be termed "abuse-labile" substances. Abuse-labile substances are pharmacological substances that have the potential for creating abusive

dependency. Abuse-labile substances can include both legal and illicit drugs.

The following are among the issues that the IRB will consider when reviewing research involving potentially addictive substances:

- (i) When this type of research is proposed, the IRB must consider the subject's capacity to provide continuous informed consent, and determine that subjects are competent and are not coerced;
- (ii) If such research involves subjects that are institutionalized, the subject's ability to exercise autonomy could be impaired;
- (iii) The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected; and
- (iv) The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.

It is critical that the IRB focus on the considerations of risk and benefit of such research.

- g. Research Involving Other Potentially Vulnerable Adult Subjects.** Employees, students, and trainees at THR and its affiliated Institutions should also be considered vulnerable subjects. Thus, the IRB should uphold the same standards in approving research involving these groups as other vulnerable subjects research.

The context of the research is an important consideration for the IRB to consider when reviewing research that involves other potentially vulnerable subjects. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and the IRB must take such considerations into account.

Educationally disadvantaged individuals should be considered vulnerable subjects. Often these individuals may speak and understand English but are unable to read. Illiterate persons may have the informed consent read to them and may "make their mark" in a manner consistent with applicable State law to document their understanding. In this situation, it is also desirable to obtain the signature of a witness to the consent process and the signature of the person conducting the consent interview. Investigators should not enroll subjects who may not truly understand what they have agreed to do.

- h. Fetal Tissue Transplantation Research.** Human fetal transplantation research supported by DHHS is governed by NIH Public Law 103-43.
- i. Research Involving Deceased Persons.** Research involving deceased persons is not covered by FDA or DHHS human subject regulations, or the Common Rule.

Chapter 16.

Research Misconduct: Allegations, Investigations and Reporting

All persons involved in research have a responsibility to foster an environment which promotes intellectual honesty and integrity, and which does not tolerate misconduct in any research activities, handling of data or any aspect of the research endeavor.

a. Research Misconduct:

Texas Health's definition of research misconduct is consistent with 42 CFR 93.103 and means "*fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results*". Research misconduct does not include honest error or opinion.

- Fabrication means making up data or results and recording or reporting them.
- Falsification means manipulating research materials, equipment or processes or changing or omitting data or results such that the research is not accurately represented in the research record.
- Plagiarism means the appropriation of another person's ideas, processes, results or words without giving appropriate credit.

b. Federal Funding Agency Requirements:

Some federal funding agencies have their own policies regarding research misconduct and require notification to the agency in the event of such an allegation or investigation. Where required, this notification will be made by the Institutional Official (IO) after consultation with Texas Health legal counsel. While federal funding agencies recognize that the primary responsibility for the prevention and detection of misconduct, and for the conduct of inquiries and investigations, rests with the institution, a number of agencies have retained the right to initiate their own investigations at any time. This policy is intended to comply with the provisions of 42 CFR Sections 93.100 through 93.319, when applicable.

c. Individual Reporting Responsibility:

Concerns about potential research misconduct should be promptly communicated to the Research Compliance Officer (RCO), via the THR System Compliance Hotline at 1-800-381-4728 or by email to SystemCompliance@texashealth.org. Reporting concerns in good faith will not jeopardize anyone's employment. Texas Health prohibits retaliation of any kind against a person who, acting in good faith, reports or provides information about suspected or alleged misconduct.

d. Inquiry

An inquiry consists of preliminary information-gathering and preliminary fact-finding to determine whether an allegation or an apparent instance of misconduct has substance. The outcome of an inquiry is a determination as to whether or not an investigation will be conducted.

e. Investigation:

An investigation is a formal examination and evaluation of relevant facts to determine whether or not misconduct has taken place.

f. Procedure for Allegations or Concerns Involving Research

- i. Upon receipt of an allegation (from any source), the RCO will assess the information presented to determine 1) whether it constitutes alleged research misconduct as defined by this policy, and 2) whether the allegation is sufficiently credible and specific so that potential evidence of research misconduct may be identified. If both of these criteria appear to be met, the RCO will notify the IO. If, the IO determines both criteria are met an inquiry will be promptly initiated. Upon initiation of an inquiry, the RCO will notify the Texas Health Chief Compliance Officer and Texas Health legal counsel who will participate as needed.
- ii. The inquiry process will be guided by the following:
 - Those conducting inquiries or investigations are promptly to take all reasonable and practical steps to obtain custody of research records and/or evidence needed to conduct the misconduct proceeding, inventory the records and evidence and safeguard them in an appropriate manner.
 - At the time of, or before the beginning of an inquiry, the accused individual (respondent) will be informed of the allegations, and be invited to comment on them. The respondent will also be provided with a copy of the draft report of the inquiry and be given an opportunity to comment on the findings for the consideration of those conducting the inquiry. In so doing, best efforts will be made (where feasible) to protect the confidence of the individual(s) who brought forward the complaint.
 - Other relevant individuals, including the complainant(s), if known, should be interviewed.

- The final report, including a recommendation as to whether or not a full investigation is warranted, will be submitted by the IO to the Research Activities and Compliance Committee (RACC) within 60 days of receipt of the allegation. If the timeframe is not possible in a particular case, the reasons are to be documented and the RACC so informed. The final report will include any comments provided by the respondent in response to the draft report.
- The documentation should include sufficient detail to permit a later assessment of the determination of whether or not a full investigation was warranted. It should describe the information reviewed, include a summary of the interviews conducted, state conclusions reached, and indicate whether or not the IO believes an investigation is warranted.
- The final report of the inquiry and a copy of the documentation will be transmitted to the RACC and maintained for seven years.
- Unless the RACC has further concerns, an IO recommendation that an investigation is not warranted will be final.

iii. Investigation Procedures

If an inquiry leads to the conclusion that an investigation is warranted, it will be guided by the following considerations:

- The formal investigation should begin within 30 days of the completion of the inquiry and after written notice to the respondent. The investigation to be completed and the final report sent to the RACC within 90 days (from start of an investigation). If an investigation cannot be completed within this time frame, the RACC should be notified. In such cases, it may be necessary for the IO to request an extension of time from federal funding agencies.
- An investigation should normally include an examination of the relevant documentation, including but not limited to relevant research data and proposals, publications, correspondence, and memoranda of telephone calls.
- Complainants, respondents and witnesses who may have information related to the matter should be interviewed. Complete written summaries of each interview should be

provided to the individual being questioned, and any comments should be appended to the summary, or reflected in a revised summary if the interviewer agrees.

- All significant issues should be pursued until there is a reasonable conclusion that all necessary and appropriate information has been amassed.
- A draft written report of findings shall be made available to the respondent with the opportunity to provide comments for the consideration of those conducting the investigation. Where identified and appropriate, complainants should also receive the portions of the draft report which concern the role or opinions they had in the investigation. Any comments on the draft from the respondent shall be appended to the final report.
- In addition to the interview summaries and comments by the respondent and respondent and complainant(s) (if applicable) on the draft report, the final written report should include: a) a description of the policies and procedures followed, b) how and from whom relevant information was obtained, and c) the findings and basis for them.
- If either the IO or the RACC considers that sanctions may be warranted, the IO shall refer the final report to the Texas Health Institution Review Board (IRB) for a determination. The report should be sufficient for the IRB to determine whether disciplinary action is called for. If any sanctions result, the IO will be informed and he/she should append that information to the final report.

g. Internal Coordination

The RCO and IO will coordinate with the Texas Health Chief Compliance Officer and Texas Health legal counsel to assure that all external notification requirements are met and to determine if any of the following emergency situations exist.

- i. An immediate health hazard, including to human or animal research subjects.
- ii. An immediate need to protect federal or Texas Health funds or equipment

- iii. An immediate need to protect the integrity of the research and/or the research misconduct proceeding
- iv. An immediate need to protect the interests of those involved in the research misconduct proceeding
- v. The likelihood that an alleged incident will be reported publicly
- vi. A reasonable indication of a possible criminal violation

In emergency situations the IO is authorized to take all appropriate actions.

h. Notification to External Agencies

Texas Health will comply with the applicable requirements and regulations of its funding agencies, and will cooperate with those agencies in regard to research misconduct.

Under circumstances not involving federal funding agencies, the IO (in consultation with Texas Health legal counsel) will make the decision whether information about the misconduct charges and their disposition will be disclosed publicly or to specific parties, including the research sponsor. This decision will normally be made upon conclusion of the final report and review with the RACC. However, if required by urgent circumstances, such a disclosure may be made at any time, by the IO in consultation with Texas Health legal counsel.

In accordance with requirements of federal funding agencies, in cases involving research funded by those agencies, the agency will be informed by the IO in the following situations.

- i. *Outcome of an Inquiry* – Federal funding agencies will be notified of the outcome of an inquiry involving funds from their agency only if that outcome includes the recommendation to conduct a full investigation.
- ii. *Commencement of an investigation* – Written notification will be provided to federal funding agencies upon determination that an investigation will be conducted. The notice will be provided on or before the commencement of the investigation and will include all information required by the agency. Generally, this notice will include at least the following: a) name(s) and position(s) of the respondent(s), b) general nature of the allegation(s), c) the agency support including any proposal or award numbers, d) the basis for the recommendation of an investigation, and e) any comments by the respondent. This information will be held in confidence to the extent permitted by law.

- iii. *Written request for time extension* – Although regulations generally permit 120 days for completion of the investigation and submission of the final report, the IO should consider whether it is advisable to request an extension of time from the agency when it appears the final report will require more than 90 days to complete. This allows 30 days for the disciplinary process, if deemed appropriate. The final report must contain a statement about the sanction (if any) imposed. An extension of time may be needed. If an extension is granted, the agency may require progress reports or the agency may undertake its own investigation prior to completion of the Texas Health investigation.
- iv. *Interim reports* – Federal agencies must be appraised during an investigation of facts that may affect current or potential funding of the individual under investigation or that may need to be disclosed in order to ensure proper use of federal funds or protection of the public interest.
- v. *Early termination* – Federal funding agencies must be notified of the final outcome of an investigation involving their funded project(s) and provided with a complete copy of the final report.
- vi. *Special emergency notifications* – In addition, federal funding agencies will be informed at any stage of an inquiry or investigation if any of the following is discovered:
 - An immediate health hazard, including an immediate need to protect human or animal subjects
 - An immediate need to protect federal or Texas Health funds or equipment
 - An immediate need to protect the integrity of the research and/or the research misconduct proceeding
 - A likelihood that an alleged incident is going to be reported publicly
 - A reasonable indication of possible criminal activity

i. Determination of Discipline

The determination as to whether discipline is to be imposed is governed by existing Texas Health policies. In cases involving medical staff members, disciplinary sanctions may only be imposed through the medical staff disciplinary process. The IO will refer cases of significant Texas Health employee misconduct to the Texas Health Chief Human Resources Officer.

Federal funding agencies have retained the right to impose additional sanctions, beyond those applied by Texas Health upon investigations or institutions. In addition, in cases where research misconduct is found, the IO may take all other appropriate actions (including correction of the public record) as deemed necessary and advisable to address the consequences of the research misconduct.

j. Cautions and Assistance

The gathering and assessing of information in cases of alleged research misconduct can be extremely difficult. It is essential to protect the professional reputations of those involved, as well as the interests of the public and of any who might be harmed by the alleged misconduct. Texas Health may use the services of a consortium or person that Texas Health reasonably determines to be qualified by practice and experience to conduct research misconduct proceedings. A consortium or person acting on behalf of Texas Health must follow the requirement of this policy. In the course of conducting inquiries or investigations, the following provisions are applicable:

- i. Expert assistance should be sought as necessary to conduct a thorough and authoritative evaluation of all evidence.
- ii. Precautions should be taken to avoid unresolved personal, professional or financial conflicts of interest on the part of those involved in the inquiry or investigation.
- iii. The anonymity of respondents and, if they wish it, the confidentiality of complainants will be protected (where feasible), and care will be taken to protect the positions and reputations of those involved in the research (including research subjects) and in the research misconduct proceeding from harm (including retaliation). Except as required in the reporting provisions above, only those directly involved in an inquiry or investigation or with a need to know should be aware that the process is being conducted or have any access to information obtained during its course. Where

Texas Health Resources
Corporate Policy for Protection of Human Research Subjects

appropriate, efforts will be made to restore the reputations of the respondent(s) when allegations are not confirmed.

Chapter 17. Managing Conflicts of Interest

Conflicts of Interest may be interpreted to include any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research.

THR Conflicts of Interest requirements are described in a separate Conflicts of Interest Policy and Procedures Manual. The Conflicts of Interest Manual should be consulted for detailed information about these requirements.

Chapter 18. How to Submit Materials to the IRB

THR has created a variety of eIRB forms to facilitate submission of materials to its IRB. The information in this Chapter will help investigators prepare materials for submission to the IRB and respond to IRB questions and requests. All forms are available on the [THR IRB website](#) and the THR eIRB system.

The goal of the IRB is to assist investigators in designing and implementing research that embodies the utmost concern for subjects' safety, dignity, privacy, and autonomy. With this goal in mind, it is fully acceptable to discuss one's research with IRB members prior to submission or at any time during the IRB review, approval, or oversight process. Advice and discussion improves quality and serves the goals of both the IRB and the investigator. The IRB staff are also available to assist investigators by answering questions or reviewing "drafts" prior to submission.

a. The eIRB and Other IRB Related Forms.

- **Form Bill 1.** Impact Assessment Form. Submit with application for initial review. This is a required form and must be on file prior to release of IRB approval for any protocol.
- **Application for Initial IRB Review.** Use eIRB forms to request initial review of research projects. In addition to basic information about the investigator and the nature of the research, this form asks the investigator to explain the research in lay terms so that the IRB can judge whether it can be approved.
- **Investigator Application for Continuing Review/Final Report.** Use the eIRB forms to request (i) continuing review of research; or (ii) project close-out when all research (including use of identifiable private information) has been completed. When the IRB approves research, it does so for an "approval period" of no longer than one year. Federal regulations do not allow for a grace period, and if research is not re-approved before the continuing review expiration date, the IRB approval expires, and all research must stop.
- **Safety/Other Reports (Unanticipated Problem/Adverse Event in Research).** Use the eIRB forms to notify the IRB promptly of reportable adverse events and/or unanticipated problems. See Chapter 9 for guidance.
- **Investigator Request for Exemption from IRB Review.** Use the eIRB application for initial review to submit proposed exempt research. The IRB determines if the research qualifies for an exemption.

- **Investigator Request for Expedited IRB Review.** Use the eIRB forms to request initial or continuing IRB review under expedited procedures. The IRB is allowed to review [nine categories of research](#) on an expedited basis. The IRB Chairperson determines if the research qualifies for expedited review and approval.
- **Amendments (Request for Modification of Approved Research).** Use the eIRB forms to request approval of any proposed changes to the research, including changes to the procedures used, the informed consent document, or advertising materials. Federal regulations require that the IRB grant prior approval for any proposed changes before they are implemented.

The IRB recommends that amendments not be submitted during the time that continuing review is being processed. This includes the time period that is within 30 days of the scheduled continuing review until receipt of final continuing review approval.

- **Request for Waiver of Informed Consent or Waiver of Documentation of Consent.** Use the eIRB forms to request waiver from the requirement to obtain (i) subjects' consent for research, or (ii) signed documentation of the consent process. The IRB may only approve such requests when specific regulatory criteria have been met.
- **Initial Review Form for Reviewers.** This form helps IRB members ensure that their initial reviews and determinations comply with Federal requirements. The form is for IRB use only, but may be of interest to investigators in understanding the IRB review process.
- **Continuing Review Form for Reviewers.** This form helps IRB members ensure that their continuing reviews and determinations comply with Federal requirements. The form is for IRB use only, but may be of interest to investigators in understanding the IRB review process.

The IRB recommends that amendments not be submitted during the time that continuing review is being processed. This includes the time period that is within 30 days of the scheduled continuing review until receipt of final continuing review approval.

- b. **Guidance for Investigators.** The IRB must review certain items at certain times depending on the type of funding an investigator receives to conduct the research. Table 18-I separates the types of investigators and the items the IRB must receive at **initial** and **continuing** review and Table 18-II provides investigators post-approval reporting requirements.

Table 18-I. Guidance for Investigators: Items to Submit for IRB Review

INITIAL REVIEW	CONTINUING REVIEW
All Human Subject Research	
<ol style="list-style-type: none"> 1. Impact Assessment (Form BILL 1) 2. Informed consent document (THR IRB template, if available) 3. Recruitment notices or ads 4. Survey instruments, psychological tests (other than standard, commercially available instruments), interview forms, scripts, etc. 5. Completion of training requirements per training policy (refer to Training Requirements for IRB Members, IRB Office Staff, Research Investigators and Research Study Staff policy) 6. Investigators' qualifications (curriculum vitae, current license information, if applicable not affiliated with THR.) 7. Formal research protocol 8. Completed THR Conflicts of Interest (COI) Form for each investigator and study staff member and, if applicable, the COI form sent to the sponsor, FDA or other agencies. 	<ol style="list-style-type: none"> 1. Current IRB-approved and stamped informed consent document 2. A list of adverse events and/or unanticipated problems involving risks to subjects or others 3. Current IRB-approved protocol with any additional IRB-approved amendments 4. Current training per training policy (refer to Training Requirements for IRB Members, IRB Office Staff, Research Investigators and Research Study Staff policy) 5. Completed THR Conflicts of Interest Form for each investigator and study staff member and, if applicable, the COI form sent to the sponsor, FDA or other agencies. 6. Copy of the latest Data Safety Monitoring/Data Monitoring Committee or equivalent report
Research with External (Federal or Non-Industry) Support	
Complete Federal or other grant application or proposal, upon notification that the project is "fundable"	
Research with FDA-Regulated Test Article and/or Industry Support	
Clinical Investigator's Brochure, Instructions for Use or Manual of Operation	Copies of all IND Safety Reports, if not already submitted to the IRB
Research with an OHRP Cooperative Protocol Research Program (CPRP)	
Research protocol and sample consent document from the sponsor or Cooperative Group	

- c. IRB Deadlines for Initial Review.** Deadlines for submitting materials to the IRB for initial review of research are provided on the [THR IRB website](#) or the [eIRB website](#).
- d. IRB Deadlines for Continuing Review.** The IRB is required to conduct substantive and meaningful continuing review of research not less than once per year. Thus, for research requiring review by the convened IRB, the IRB approval period for research may extend no more than 365 days after the convened meeting at which the research was last approved. For research within categories appropriate for expedited review, the IRB approval period may extend no more than 365 days after the expedited review at which the research was last approved.

The regulations permit no grace period to this one year requirement. Research that continues after the approval period expires is research conducted without IRB approval. Since the research must be re-approved before the expiration deadline, investigators should ensure that the IRB receives continuing review information for an IRB meeting prior to the expiration date. For instance, if the IRB originally approved a research project on May 30, 2001 for a period of one year, the research will expire on May 29, 2002. The closest IRB meeting to that date is June 5, 2002. However, the IRB must review and approve the research before it expires. Thus, the investigator must ensure the IRB reviews and approves the research at its meeting on May 5, 2002. Since the IRB may require additional information or changes before approving the continuing review application, the application should be submitted in time to be considered at the meeting preceding the May 5th meeting.

The IRB will automatically stop the enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in expired research only where the IRB determines that continued involvement is in the best interest of the subjects. Refer to Chapter 9 for detailed information.

- e. Communication of Determinations.** For full (convened) reviews, the IRB should ordinarily notify the investigator of its determinations in writing within 5-7 working days after its meeting. For expedited reviews, the IRB should ordinarily notify the investigator of its determinations in writing within 5-7 working days after receiving a complete submission of all required materials.

Table 18-II

Summary Table of Post-Approval Reporting Requirements for Investigators

Type of Report	What and/or When to Report	
Notice of Unanticipated Problems and Adverse Events		
Adverse Events (AEs)/Incidents	Reporting Criteria	When to Report
Internal Subject death	Related or possibly related and Unexpected = Unexpected Problem	Report within 24 hours of the PI awareness
External or Internal Adverse Events/incidents that the PI determines are unanticipated problems (UPs)	Related or possibly related and Unexpected and Serious = Unexpected Problem	Report within 10 working days of the PI awareness
Internal events/incidents involving a human gene transfer protocol that the PI determines	Serious adverse event	Report immediately
External events that the PI or Sponsor determines	<ul style="list-style-type: none"> • Changes the study risks or benefits, OR • Necessitates a modification to the THR-approved consent document(s), and/or the THR- 	Report within 10 working days of PI awareness

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

	approved application/protocol	
External events that the PI or Sponsor determines	Do not qualify as an Unexpected Problem (Related or Possibly Related, Unexpected, and Serious)	<u>Do not</u> need to be reported to the IRB promptly or periodically at the time of continuing review.
Internal AEs/SAEs/Subject Deaths that the PI or Sponsor determines	Do not qualify as an Unexpected Problem (i.e. they are not Related or Possibly Related, <u>and</u> Unexpected, <u>and</u> Serious)	Do not need to be promptly reported to the IRB. These events can be reported periodically at the time of continuing review. If the Sponsor requires prompt reporting the IRB will issue an acknowledgement of receipt of the report.
Other Internal or External Unanticipated Problems that are not Adverse Events (includes study suspensions, hold or termination – refer to Chapter 9/Section I/iv for additional examples)	Related, probably or possibly related and Unexpected and Serious = Unexpected Problem	Report within 10 working days of the PI awareness
<p>Note: Definitions for relatedness, unexpected and serious can be found in the THR IRB Glossary. Go to the THR IRB website at www.texashealth.org/irb, policies section or click here to access the Glossary.</p>		
<p>Other Types of Events or Updated Safety Information</p>		

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

DSMB/DMC reports and IND or other safety reports that provide new information about the study	Report within 10 working days of receipt by PI
Any reports, audit findings, or correspondence to or from any regulatory agency	Report within 10 working days of the PI awareness
Other safety information or publication that suggests a change to the risk or benefit of the research	Report within 10 working days of the PI awareness
Protocol Deviations, Violations, Incidents including Subject Complaints	
Emergent protocol deviations/violations	Report within 5 working days of the PI awareness
Non-emergent protocol deviations/violations	Report within 10 working days of the PI awareness
Study Approval Lapse/Final Report/No Activity	
Lapse in IRB approval	IRB approval must be reinstated within 90 days
Continuation of study activities post study expiration	As soon as possible/submit criteria noted in Section r of Chapter 9
Notice of completion, discontinuance of project or withdrawal of exemption	Within 90 days after the completion or discontinuance of a research project or of withdrawal of the exemption for a research project
If applicable, the investigator shall report any findings from a closed study when those affect the safety and medical care of past subjects	Findings will be reported for 2 years after the closure of the study
Studies in an eIRB Pre-submission State (not formally submitted)	Withdrawn 180 days (approximately 6 months) from creation of study
Emergency Use	
Emergency use of a test article	Report within 5 working days of the use of the test article

**Table 18-IV
Risk Determination for Continuing Review**

Risk Level	Descriptor	Continuing Review Cycle
Minimal (Level 1)	The probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests. No serious adverse events are anticipated.	Annual (12 month cycle)
Low (Level 2)	Involves a minor increase over minimal risk- the intervention or procedure presents experiences that are reasonable commensurate with those inherent in actual or expected medical, dental, physiological, social or educational situations.	Annual (12 month cycle)
Moderate (Level 3)	Clearly an elevated level of potential harm (physical, psychological, legal, occupational, reputation, etc.) to subject; however, risks are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.	Annual (12 month cycle)
High/Significant (Level 4)	Involves greater than minimal risk with no prospect of direct benefit to individual subjects, but is likely to yield generalized knowledge about the subject's disorder or condition. Studies that are high levels of risk may result in permanent physical and/or mental changes, hospitalization, and/or death.*	Semi-annual (6 month cycle)

*Texas Health Resources
Corporate Policy for Protection of Human Research Subjects*

<p>Minimal, Low and Moderate risk protocols will be reviewed <u>annually</u> by the THR IRB unless there are specific factors which suggest the need for more frequent review. High risk protocols may be reviewed more frequently as designated by the IRB. The examples cited after each level of risk category is to be used as a general guide.</p>
<p>NOTE that other factors may influence risk assignment and must be taken into consideration:</p> <ul style="list-style-type: none">• Potentials for invasion of privacy/breach of confidentiality• The psychological impact of protocol• Social implications• Potential for conflicts of interest, etc.
<p>Vulnerable populations such as children, pregnant women, elderly, psychologically or neurologically impaired, and prisoners will be assessed for participation by the level of risk and not solely on their specific vulnerable category.</p>
<p>*Examples of Level 4 (<i>significant level of</i>) risk are those that may result in permanent physical and/or mental changes, hospitalization, and/or death:</p> <ul style="list-style-type: none">• An investigator-initiated IND trial• Involves an intervention or invasive procedure with substantial risk• Implantation of device with IDE• Involves the use of a new chemical or drug for which there is little or no toxicology data in humans• Gene therapy study or research involving recombinant DNA molecules (gene transfer)• An investigator initiated multi-center trial• Investigator initiated phase III clinical trial• Involves the manufacturing of agents on campus• Study has provisions to waive consent in emergency circumstances• Blinded Phase I and II trials• Phase I or II studies with no available safety data in humans

Table 18-V
The THR IRB Review Process

