



Investigator Manual for Clinical Research

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Section I Introduction

1.0 Defining Human Research

- 1.1 Human Subject Research
 - 1.2 Research Roles
-

1.1 HUMAN SUBJECT RESEARCH

Definition of Terms

Children’s Healthcare of Atlanta (Children’s) adopts the federal Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) regulatory terminology for defining human subject research, as follows:

“*Research*” is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45§46.102(d)). Examples of systematic investigations include:

- Clinical trials of drugs or devices
- Medical outcomes study comparing approved drugs or devices
- Surveys and questionnaires
- Interviews and focus groups
- Analyses of existing data or biological specimens
- Epidemiological studies
- Evaluations of social or educational programs
- Cognitive and perceptual experiments
- Medical chart review studies

“*Human subject*” means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (45§46.102(f)). This may be 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 human or a patient (21§50.3(g)).

- “*Intervention*” includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes (45§46.102(f)).
- “*Interaction*” includes communication or interpersonal contact between investigator and subject (45§46.102(f)).
- “*Private information*” includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (45§46.102(f)).

- “*Test article*” means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation from the Public Health Service Act (21§50.3(j)).

Research results do not have to be published or presented at a professional meeting to be defined as human subject research. The intent to contribute to “generalizable (scholarly) knowledge” makes an activity research, regardless of publication. Research that never is published is still research.

All human subject research activities in which Children’s is engaged, regardless of sponsorship and overall intent, must be submitted to the Children’s Clinical Research department through the Children’s Institutional Review Board (IRB) office. The human subject research may not be initiated until approval is issued by the Children’s Director of Clinical Research, Manager of Operations and Finance, and the appropriate IRB(s).

1.2 RESEARCH ROLES

Research Roles and Responsibilities

Human subject protection is a shared responsibility of all individuals and organizations involved in research. These entities include the federal agencies that enforce the human subject research regulations, the institutions engaged in human subject research, the IRBs reviewing the human subject research and the investigators conducting the human subject research. The roles and responsibilities of these different entities are defined in federal and state laws and regulations pertaining to human subject research.

Summary:

Institution

- Children’s bears responsibility for compliance with the DHHS and FDA regulations for the performance of all human subject research activities in which it is engaged.
- Children’s is required to use additional safeguards for research in vulnerable populations (e.g., children). This is true for research conducted at sites managed with the direction of any employee or agent of Children’s.
- Children’s has responsibility for educating researchers on issues of research ethics and scientific integrity.
- Children’s has a mandated responsibility to investigate alleged cases of scientific misconduct. In addition, Children’s has a responsibility to have and enforce a policy on conflict of interest.
- Children’s has responsibility for establishing and maintaining procedures to ensure appropriate ethical review of research proposals by the IRB, administrative review of research protocols, contracts and grants by the Clinical Research department, and scientific peer review as needed.

Signatory Official

- Allocates necessary resources to the human subject protection program to ensure its success.
- Completes the training requirements for education in human subject protection.
- Has regular communication regarding the status of the human subject protection program and, as necessary, individual studies.

Institutional Review Board (IRB)

- Ensures compliance with the Children's policies and procedures, federal regulations, and state and local laws relative to the review of human subject research studies.
- Reviews all research activities involving human subjects and documents the findings regarding ethical considerations, scientific merit, and adherence to federal regulations and IRB policies and procedures.
- Reviews research activities to ensure that:
 - Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
 - Risks to subjects are reasonable in relation to anticipated benefits, if any, and to the importance of the expected knowledge. In evaluating risks and benefits, the IRB considers only those risks and benefits that may result directly from the research (as distinguished from risks and benefits that people would have even if not participating in the research); and
 - Selection of subjects is equitable. In making this assessment, the IRB takes into account the purpose(s) of the research and the setting in which the research will be conducted;
 - Informed consent is obtained from the subject or the subject's legally authorized representative and appropriately documented, unless waived in accordance with applicable federal regulations;
 - Where appropriate, the research plan makes provisions for monitoring the data collected to ensure the safety of subjects; and
 - Where appropriate, there are provisions to protect the privacy of participants and to maintain the confidentiality of data.
 - Where appropriate, additional safeguards are included in the study to protect the rights and welfare of subjects when some or all of them are likely to be vulnerable to coercion or undue influence (children, prisoners, pregnant women, handicapped, mentally disabled persons, or economically or educationally disadvantaged persons).
- Reviews research protocols and is authorized to approve, require modifications to secure approval, disapprove, and terminate or suspend.
- Conducts continuing reviews of approved research. Reviews proposed amendments, adverse events, protocol deviations and matters of noncompliance.
- Has the authority to:
 - Require research progress reports;
 - Audit and/or monitor the research and researchers for adherence to the federal regulations, Children's policies and IRB policies and procedures; and
 - Report suspensions, terminations, and noncompliance to IRB officials, the Children's officials, research administrative (RA) officials, and the federal government.
- Completes all training requirements and stay informed of current research-related and regulatory developments.

IRB Administrative Staff

- With the IRB, responsible for maintaining the Children's Federal Wide Assurance (FWA) and for ensuring compliance with its terms.

- Responsible for compliance with the Children's policies and procedures, federal regulations, and state and local laws relative to the conduct of human subjects research studies.
- Provides guidance regarding the interpretation of regulations, laws, and policies to the organization's researchers, staff and administrators.
- Develops and implements the Children's human subject protection policies and procedures.
- Completes all required human subject protection training requirements and, if applicable, Health Insurance Portability and Accountability Act (HIPAA) training, and ensures that investigators and key study personnel complete required training.
- Responsible for providing opportunities for human subject protection training to investigators, key study personnel, the Signatory Official, and all the Children's staff who participate in the human subject protection program.
- Performs quality assurance monitoring of research protocols and investigates matters of noncompliance. Implements corrective action as needed in accordance with the Children's policies and IRB policies and procedures.
- Monitors federal regulatory Web sites and other research-related resources to stay current with regulatory changes in human subject protection guidelines and policies. Communicates pertinent information to staff in a timely manner.
- Maintains all study-related documentation in accordance with the Children's policies, IRB policies and federal regulations.

Principal Investigator (PI)

- Oversees and conducts the research process and is responsible for the conduct of the investigators and research staff at all study sites for which he/she is listed as the Principal Investigator.
- Ensures compliance with research protocols, and applicable federal, state, and local laws and regulations, the Children's policies, and IRB policies and procedures.
- Responsible for the safety and welfare of subjects.
- Ensures compliance with the protocol's data and safety monitoring plan, and reports adverse events to the IRB, study sponsor and appropriate federal agencies.
- Ensures that informed consent is appropriately obtained from all subjects and that subjects are treated with respect and dignity.
- Completes all required human subjects protection training, and, HIPAA training, and ensures that investigators and key study personnel complete required training.
- Reviews all IRB policies and procedures as part of the required initial training for conducting human subject research. Routinely reviews the IRB Web site for new or revised IRB policies and procedures.
- Reviews scientific literature to ensure that protocol interventions are consistent with current research data and do not place subjects at unnecessary risk.
- Is responsible for the adequacy of all submissions to the IRB including protocol applications, amendments and adverse event reports.
- Ensures the timely continuing review of protocols and the submission of all re-approval applications before the protocol's expiration date. Reports protocol expirations promptly to the IRB.

- Submits proposed changes to the research in the form of protocol amendments to the IRB before the changes are implemented, except when such changes must be implemented immediately to ensure the health and well-being of research subjects.
- Responsible for the protection of subjects' privacy and confidentiality according to applicable HIPAA policies, the Children's policies, and IRB policies and procedures.
- Maintains all study-related documentation in accordance with the Children's policies, IRB policies and federal regulations.

Co-investigator (or Sub-investigator)

- Records and maintains accurate documentation of all activities in compliance with federal, institutional and sponsor requirements, including collecting data using case report forms and maintaining appropriate source documents.
- Recruits and screens research subjects according to the inclusion/exclusion criteria.
- When requested, obtains appropriate informed consent from all subjects and in doing so treat subjects with respect and dignity.
- Where applicable, ensures proper use of randomization schedules.
- Carries out the protocol-specified procedures and adhere to the protocol-defined timelines.
- Secures and controls the use of the investigational agent(s) or device(s).
- Reports all adverse events and unanticipated problems according to the requirements of federal regulatory agencies, the IRB and the study protocol.
- Tracks financials and ensures payments are made to suppliers and providers of services for the research.
- Complies with the IRB-approved research protocols, applicable federal, state and local laws and regulations, the Children's policies, and IRB policies and procedures (this includes ensuring all appropriate approvals are obtained prior to initiation of the research).
- Completes all required human subject protection training, and, if applicable, HIPAA training.
- Protects subjects' privacy and confidentiality according to applicable HIPAA policies, the Children's policies, and IRB policies and procedures.
- Fulfills commitments made to the sponsor and/or to the FDA (e.g., form 1572 or the Investigative Agreement).

Coordinator

- Maintains data pertaining to research projects, completes source documents/case report forms and performs data entry. Prepares research case reports in quantitative measures and narrative form.
- Assists with patient recruitment and enrollment.
- Attends study meetings.
- Reviews medical records and/or conducts screenings for recruitment of study participants, performs interviews and conducts questionnaires. Gathers, coordinates and processes pertinent data specific to each research project.
- Collects study specimen according to protocol which may include phlebotomy, processing and preparation for shipping.
- Assists with literature search and protocol development
- Coordinates services, schedules procedures, creates and maintains case packages, and monitors charges.

- Assists with quality assurance and tracks regulatory submissions.
- Interfaces with study sponsors, monitors and reports Serious Adverse Events (SAE), and resolves study queries.
- Completes IRB submissions and presents reports to supervisor.
- Routinely reviews the IRB Web site for new or revised IRB policies and procedures.
- Orders and maintains equipment and supplies.
- Participates in on-call schedule as needed.

2.0 Regulations and Ethical Considerations

- 2.1 Federal Regulations
 - 2.2 Federal Agency Oversight
 - 2.3 Ethical Considerations
 - 2.4 Vulnerable Populations
 - 2.5 Risks to Subjects
 - 2.6 Conflict of Interest
-

2.1 FEDERAL REGULATIONS

Federal Regulations Governing Human Subject Research

21 CFR 50 (FDA):

Protection of Human Subjects

- Applies to all clinical investigations regulated by the FDA by the federal Food, Drug and Cosmetic Act as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA (including food and color additives; drugs, medical devices and biological products for human use; and electronic products)
- Describes the informed consent requirements

45 CFR 46 (HHS):

Protection of Human Subjects

- Applies to all research receiving federal funding. Institutions that receive federal funding may also choose to have it apply to all types of research being conducted.
- Divided into several parts:
 - Part A = "The Common Rule"
 - Parts B, C and D = "Vulnerable" Populations

Federal Regulations Governing IRBs

**21 CFR 56 (FDA):
IRBs**

- For IRBs that review FDA-regulated clinical research studies
- Describes:
 - Circumstances where IRB review required or exemption or waiver may be granted
 - Criteria for approval, expedited review procedures, and circumstances for suspension or termination
 - Requirements for record keeping and reporting noncompliance

Federal Regulations Governing New Drug Application/ Investigational Device Exemptions

21 CFR 314 (FDA):

Applications for FDA Approval to Market a New Drug

- Purpose is to establish an efficient and thorough drug review process in order to: (a) facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective.
- Also intended to establish an effective system for the FDA surveillance of marketed drugs.

21 CFR 312 (FDA):

Investigational New Drug (IND) Application

- Sponsors may have to submit an IND application to the FDA if they intend to test a drug's safety or efficacy.
- Not required if it: (1) is not meant to be reported to support new indication for use or other labeling info; (2) is not intended to support big change in advertising; (3) does not involve significant increase in risks; (4) is conducted in compliance with the IRB review and consent requirements; (5) is conducted in compliance with promotion and sale requirements; AND (6) does not intend to invoke an exception from informed consent requirements for emergency research.

21 CFR 812 (FDA):

Investigational Device Exemptions (IDE)

- Sponsors may have to submit an IDE application to the FDA if they intend to test the safety or efficacy of a medical device.
- Medical device = "a healthcare product which does not achieve its primary intended purpose by chemical action or by being metabolized."
Ex: surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, orthopaedic pins and diagnostic aids.

- Significant risk (SR) or nonsignificant risk (NSR): Determination is initially made by the sponsor. SR goes to FDA and IRB. NSR goes just to IRB. Risk determination should be based on the proposed use of the device in an investigation, not just on the device alone.

2.2 FEDERAL AGENCY OVERSIGHT

The Department of Health and Human Services (HHS) Public Health Service (PHS) oversees many other departments within the federal government. PHS is the government's principal agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves.

HHS controls more than 300 programs/agencies and the largest grant-making agency in the federal government.

HHS Agencies:

- Food And Drug Administration (FDA)
- Office of the Secretary of Health and Human Services (OS)
- National Institute of Health (NIH)
- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare and Medicaid Services (CMS)
- Health Resources and Services Administration (HRSA)
- Agency for Healthcare Research and Quality (AHRQ)

2.3 ETHICAL CONSIDERATIONS

Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. *Respect for Persons*—Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.
2. *Beneficence*—Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.
3. *Justice*—Who ought to receive the benefits of research and bear its burdens? There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed.

These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Unethical practices to avoid (among others):

- Lack of informed consent
- Coercion or undue pressure on volunteers (or on a parent to volunteer their child)
- Use of a vulnerable population
- Exploitation of a vulnerable population
- Withholding information
- Withholding available treatment
- Withholding information about risks
- Putting subjects at risk
- Risks to subjects outweigh benefits
- Deception
- Violation of rights

2.4 VULNERABLE POPULATIONS

The concept of subject vulnerability is important to research ethics and to regulatory compliance 45 CFR 46 Subparts require that “when some or all of the subjects’ coercion or undue influence, additional safeguards have been included in the study to protect the subjects.” Vulnerable Populations are subjects who have limitations on either capacity or voluntariness, thus having the potential to have their rights abused in the following ways: physical control, coercion, undue influence and manipulation. The federal government defines vulnerable subjects as, children, embryos and fetuses, mentally disabled individuals and prisoners. **Children’s Healthcare of Atlanta is a pediatric healthcare system; therefore, all patients belong to the vulnerable population’s category which garners them additional law protections.** Additional protections for children are detailed in 45 CFR 46 Subpart D.

2.5 RISKS TO SUBJECTS

Definition of “Benefit”

A benefit is the positive value or advantage of being part of the research study. This value or advantage might be concrete for individual subjects, like a greater chance of having a good therapeutic outcome. Alternatively, it might be more intangible and general. For example, the results from a study could be crucial to understanding the underlying socioeconomic causes of drug addiction.

Definition of “Risk”

Risks generally are evaluated according to the probability and magnitude of any harm that might occur. Will the risk occur in almost all subjects or in only one of 10,000 subjects? We can also quantify risk according to the magnitude of harm. Will the harm consist of some minor itchiness, or will some subjects die? Risks can also be classified according to their type. In medical research we often focus on physical risk. However, risks may also be social, legal, economic or

psychological in nature. In addition, risks may apply to the individual subject or may apply to a broader segment of the society.

Balancing Potential Benefits and Risks

Risks to the subject or society must be weighed against potential benefits. The probability of harm relative to the probability of benefit should be determined, as well as the relative magnitude of risks and possible benefits. As an aside, payment for study participation should never be considered a benefit. One of the most difficult things that researchers and IRBs have to do is to determine that the potential benefits of the outcomes of the research outweigh the risks of conducting the research. This is difficult because neither the potential benefits nor risks can be known ahead of time. The risks are assumed by individuals, while the benefits may accrue to society at large rather than to individuals.

Any IRB dealing with pediatric studies must evaluate the studies into specific risk categories:

- **Category I: Minimal Risk**
Approvable if the IRB finds and documents that adequate steps were taken to obtain the child's assent.
- **Category II: Greater than minimal risk, but present a prospect of direct benefit to the subject.**
Approvable if the IRB determines that the anticipated benefit justifies the risk, and that it is at least as favorable as the benefits of alternative treatments.
- **Category III: Greater than minimal risk and no direct benefits to subject, but are likely to yield generalized knowledge about the condition being studied.**
Approvable only if the risk is a "minor increase greater than minimal risk" and the test procedure will produce knowledge that is of "vital importance" to society.
- **Category IV: Not otherwise approvable, but presents an opportunity to understand, prevent or alleviate a serious problem affecting the health and welfare of children**
Approvable only after consultation with FDA Commissioner and expert advisory panel, and an opportunity for public discussion.

Permission from a parent/legal guardian is always required when a child is enrolled in a study.

Categories I and II—one parent can sign if that is consistent with state laws and IRB requirements.

Categories III and IV both parents/guardian are required to sign, unless there is adequate justification why there is only one parent.

Assent is required unless the child is too young (less than 6 years) to understand the consent process or if the study offers a benefit unavailable elsewhere. Assent

can be waived if the study is no more than minimal risk and study cannot be conducted without the waiver. Assent is not required if the patient is unable to provide it due to medical condition or developmental age is less than 6 years.

- } For more information on assenting a patient, refer to policy 1.61 Assent and Legally Authorized Representative Permission in Pediatric Research on the Clinical Research Web site on Careforce Connection:
<http://careforce/cms/default.aspx?id=2057>

2.6 CONFLICT OF INTEREST

A Conflict of Interest—A conflict of interest is a set of conditions in which professional judgment concerning a primary interest such as a patient’s welfare or the validity of research could be unduly influenced by a secondary interest such as financial gain. The secondary interest is not always judged to be good or bad. Often the secondary interest is a legitimate, necessary aspect of professional life, e.g., compensation for time spent conducting research. Conflicts of interest may affect individuals, an institution, or both. Further, there is often no certainty that a set of conditions will in fact unduly influence professional judgment. Thus, the term *potential conflict of interest* is often used.

Potential conflicts of interest include situations in which an investigator:

- Has a consulting relationship with the sponsor of his or her research.
- Have equity interests (stock, stock options, stock warrants) in the company sponsoring his or her research. Note: Interests in mutual funds are generally acceptable and not viewed as potential conflicts of interest.
- Is the inventor of the technology being studied or of a tool used in the trial
- Owns the patent for the technology being studied.
- Is a member of the Board of Directors or an Officer of the corporation sponsoring the research

NOTE: The term individual investigator includes the investigator, spouse or dependent children, and any members of the research team (co-investigators, nurses, technicians or research staff members) who are responsible for the design, conduct or reporting of the research.

Current Requirements Applicable to Individual Investigators

Before beginning a study, individual investigators are required to disclose financial interests that may be affected by the outcome of research to the IRB when submitting the research proposal.

The FDA requires sponsors and individual investigators to report certain financial arrangements as part of marketing applications for drugs, biologics and medical devices [Title 21CFR, Section 54; Part 4].

3.0 *The Children’s Healthcare of Atlanta Research Infrastructure*

3.1 Human Research Protection Program

3.1 HUMAN RESEARCH PROTECTION PROGRAM

Children's has adopted the Human Research Protection Program created by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) as the standard for protection of human subjects. The program contents include:

Organization

- Establishing a formal process to monitor, evaluate and continually improve the protection of human research participants.
- Dedicating resources sufficient to do so.
- Exercising oversight of research protection.
- Educating investigators and research staff about their ethical responsibility to protect research participants.
- Providing a mechanism to intervene to research and to respond directly to concerns of research participants.

IRB

- Created to provide ethical review and oversight of research.
- Mechanisms are in place to ensure the independence of its ethical review and oversight functions from other units within the organization, particularly with respect to decision-making regarding the ethics of research involving human participants.
- IRB structure, composition, operations and review standards are set forth in federal regulations.
- IRB determines that the risks of proposed research are reasonable in relation to the potential benefits to the participants and to society, and the risks are minimized to the extent possible consistent with sound research design.
- IRB has an ongoing responsibility for approved research to oversee that the welfare of the participants is protected and to determine that the risks and potential benefits remain reasonable.

Investigator

- The standards set forth requirements for Investigators and other research staff involved in research involving human participants.
- Clinical Research ascertains and enhances the competence of its Investigators through educational tools and classes.

Sponsored Research

- Children's identifies and addresses human protection requirements with all sponsors.
- Requirements include, but are not limited to, the ethical conduct of research, dissemination of knowledge gained from research, and the availability of healthcare to injured research participants.

- Children’s applies its Human Research Protection Program to all sponsored research.

Participant Outreach

- Children’s has channels for receiving and responding to participant and community concerns and questions about research and conducts outreach and education activities with participants and their communities.
- Children’s encourages the involvement of the research participant and the public in building research programs thus enhancing trust in the conduct of research and the desire to help investigators pursue sound, ethical science.

3.2 CORE OFFICES

The Clinical Research department is located among three campuses:

1. The Children’s Office Park—Clinical Research Administration
1711 Tullie Circle
Atlanta, GA 30329-2303
2. Children’s at Egleston—various locations within the hospital
1405 Clifton Road NE
Atlanta, GA 30322-1062
3. Children’s at Scottish Rite—various locations within the hospital
1001 Johnson Ferry Road NE
Atlanta, GA 30342-1600

Specific phone numbers are available at:

Careforce/Departments/Clinical Research/Contacts

<http://careforce/cms/default.aspx?id=159>

Section II Study Preparation

4.0 Study Feasibility Assessment

- 4.1 Scientific Validity
 - 4.2 Resource Assessment
 - 4.3 Recruitment Potential
 - 4.4 Financial Feasibility
-

4.1 SCIENTIFIC VALIDITY

Each proposed protocol should be reviewed by the investigator for scientific validity. Key items to consider:

- Literature Review: Identify gaps in literature and verify that literature supports need for further research.
- Research Design: Clearly state hypothesis, adequacy of experimental, quasi-experimental or nonexperimental design (i.e. design/methods is consistent with research questions; methods are clear, comprehensive and easy to follow). Protocol should include hypothesis, specific aims, background and significance, materials and methods, inclusion and exclusion criteria, analysis plan, and references.
- Measurement (Instruments/Data Collection): Verify adequacy and appropriateness of data collection and/or biochemical analysis methods, reliability and validity of instruments/data collection tools.
- Sample Size/Composition: Identify adequate number of patients, definition of study population and adequate power for study design.

4.2 RESOURCE ASSESSMENT

- Background and experience of investigators.
- Background and experience of coordinators.
- Appropriate facilities—laboratory services, other support services, equipment and personnel available to conduct research.

4.3 RECRUITMENT POTENTIAL

- Patient population meeting inclusion criteria available in geographic area.
- Number of additional visits required.
- Compensation for time and travel included.
- Burden on patient and family.

4.4 FINANCIAL FEASIBILITY

- Does the proposed budget meet the cost of participation?
 - Things to consider:
 1. Time requirement for investigator/coordinator: When considering time requirements assess all study-related activities—study preparation, staff education, maintaining regulatory readiness including IRB, managing communications with sponsor, patient enrollment and follow-up, study document completion, monitoring visits, etc.
 2. Support services required such as laboratory or radiology: Does the proposed budget cover the institutional costs of required tests or procedures and associated professional fees (when applicable)?

3. Additional required services and costs, such as statistical support and institutional indirect cost rate.

5.0 Education and Training

- 5.1 Required Research Training
- 5.2 Additional Training Opportunities
- 5.3 Professional Research Associations

Children's Healthcare of Atlanta requires training program completions for clinical researchers. The successful completion of applicable training programs is required before an individual is permitted to participate with a clinical research team. Some training programs are required of all researchers, whereas others are only required in certain circumstances and is explained in more detail below. The training programs include the following:

- A. Human Subjects Research Education Certification Program (CITI)
- B. Environmental Health and Safety Training
- C. The Children's Manual for Clinical Research
- D. Clinical Research Standard Operating Procedure (SOP) Training
- E. SiteMinder® Training

5.1 REQUIRED RESEARCH TRAINING

A. Human Subjects Research Education Certification Program (CITI)

To help ensure that clinical research personnel know the requirements for the protection of human subjects, Children's Healthcare of Atlanta has established relevant training requirements and a minimum test score. All key research personnel involved in human subjects research, including all those listed on the IRB submission, must each individually and independently complete the CITI course as instructed on the IRB Web site. Key personnel include:

- Principal Investigators
- Co-investigators
- Research Coordinators
- Research team members who have contact with research participants
- Research team members who have access to subject research data and identifiers of subjects

Learning Objectives

The specific learning objectives for the basic course are to provide the target audience with:

- An understanding of the historical perspectives, ethical principles and federal regulations associated with the conduct of research with human subjects.
- A clear understanding of what constitutes human subject research and how informed consent must be applied in human subject research.

- Basic information on the regulations and policies governing research with investigational drugs, biologics and devices and how the findings of The International Commission on Harmonization (ICH) affect the conduct of research with human subjects throughout the world.
- A basic understanding of the risks to privacy and confidentiality of human subjects who participate in social and behavioral research.
- An understanding of the special considerations that must be addressed when "vulnerable populations" such as prisoners, minors, pregnant women and fetuses in utero are used in research activities.
- An understanding of how to recognize and avoid conflicts of interest in human subject research.
- New insights into the concept of group harms in vulnerable populations such as minorities and workers in a workplace setting and the use of community consultation to prevent injury to special social structures.
- An understanding of the special risks facing human subjects when they participate in research conducted through the Internet.
- A clear understanding of the ethical issues and federal regulations in force during the conduct of social or behavioral research, records based research and genetics research with human subjects.
- An understanding of the policies, regulations and risks associated with conducting research with children in a public school setting.
- A clear understanding of the special procedural and regulatory policies for human subject research at Veterans Administration research facilities.
- New information on late-breaking topics that may affect the use of human subjects in research. The intent is to provide the user with the latest guidance from regulatory agencies and to provide timely information about new human subject issues.

Steps For Completing All Necessary CITI Modules

If Children's Healthcare of Atlanta is your primary affiliation and you have no other affiliation with another institution:

1. Go to www.citiprogram.org
2. Select "New Users—Register Here"
3. Select "Participating Institution—Children's Healthcare—Atlanta"
4. Type in your chosen user name and password
5. Type in your first name, last name and e-mail address
6. Click "Submit"
7. Complete the member information
8. Answer the questions about the type of research you will be performing/participating
9. Click "Main Menu"
10. Under "Status" of "My Courses" click "Enter" to begin modules

If Children's Healthcare of Atlanta is your primary affiliation but you are doing research with Emory:

1. Go to www.citiprogram.org
2. Select "New User—Register Here"
3. Select "Participating Institution—Children's Healthcare—Atlanta"

4. Type in your chosen user name and password
5. Type in your first name, last name and e-mail address
6. Click "Submit"
7. Complete the member information
8. Answer the questions about the type of research you will be performing/participating
9. Click "Affiliate with another institution"
10. Select "Participating Institution—Emory University" and click submit
11. Complete the member information
12. Scroll down to complete "CITI Course Enrollment Questions" section and click "Continue"
13. Click "Main Menu"
14. Under "Status" of "My Courses" click "Enter" to begin modules

If Emory is your primary affiliation but you are doing research with Children's Healthcare of Atlanta:

1. Go to www.citiprogram.org
2. Select "New User—Register Here"
3. Select "Participating Institution—Emory University"
4. Type in your chosen user name and password a
5. Type in your first name, last name and e-mail address
6. Click submit
7. Complete the member information
8. Scroll down to complete "CITI Course Enrollment Questions" section and click "Continue"
9. Click "Yes" to affiliate with another institution
10. Select "Participating Institution—Children's Healthcare—Atlanta"
11. Type in your chosen user name and password
12. Type in your first name, last name and e-mail address
13. Click submit
14. Complete the member information
15. Answer the questions about the type of research you will be performing/participating
16. Click "No" if all affiliations have been entered
17. Under "Status" of "My Courses" click "Enter" to begin modules

B. Environmental Health and Safety Training

Laboratory Safety Training: All new employees receive an overview of hazardous chemical safety training during new employee orientation. Departments are responsible for identifying the training needs of their employees.

Packaging and Shipping Infectious Substance Training: According to the International Air Transport Association (IATA), individuals who pack and/or ship infectious agents, including human blood, tissue or body fluids, must be trained every two years.

Departmental training, individual computer training and special training session on Laboratory Safety or specific topics, e.g., blood borne pathogens or chemical safety, may be arranged on a case-by-case basis in coordination with the Clinical Research department, Laboratory department, Learning Services, or other applicable departments at Children's Healthcare of Atlanta.

C. The Children's Manual for Clinical Research

All investigators (including Principal Investigators and Co-investigators) and study staff (including Research Coordinators) must complete a review of the Children's Manual for Clinical Research prior to conducting research at/for Children's Healthcare of Atlanta. The purpose of this manual is to assist in providing well-rounded and adequate knowledge of clinical research conduction, and to serve as a reference for study staff. A copy of this manual can be obtained through the Clinical Research department at Children's Healthcare of Atlanta—online or CD.

D. Clinical Research Standard Operating Procedures (SOP) and Policies

All investigators (including Principal Investigators and Co-investigators) and study staff (including Research Coordinators) must complete a review of the Clinical Research Policy and Procedures at Children's Healthcare of Atlanta prior to conducting research. The purpose of these policies and procedures is to provide information regarding standards policies as they relate to conducting clinical research at Children's Healthcare of Atlanta, and to serve as a reference for study staff. All policies are located at Careforce Connection in the Clinical Research department at Children's Healthcare of Atlanta.

E. SiteMinder® Training

Emory's clinical trial researchers and study staff must use Oracle Clinical SiteMinder. SiteMinder (a software application licensed from Oracle by Emory University School of Medicine) facilitates the management of nonclinical aspects of clinical trials: administrative, regulatory and financial.

- SiteMinder is used to create and manage budgets; to track and manage study subject visits; and to create and track expenses, invoices, payments and income received.
- Before using SiteMinder, the clinical trial researchers and study staff must complete a one-day training program conducted by the Clinical Trials Office (CTO) at Emory University. Class schedules and details about training and registration are listed on the Emory University Web site <http://www.med.emory.edu/research/cto/>.
- Additional SiteMinder training is available to those who have completed the basic training. These additional training sessions provide an opportunity to work with an instructor, e.g., one-on-one assistance in setting up a clinical trial and entering study data in SiteMinder.
- The mandate to use the SiteMinder software system for the management of clinical trials being conducted within Emory Healthcare or an Emory Affiliate applies only to those trials initiated after May 31, 2004. For any trial that began before this cutoff date, the Principal Investigator is not required to enter data into the SiteMinder database.

5.2 ADDITIONAL TRAINING OPPORTUNITIES

Research Coordinators' Forums set up by the Clinical Research department occur quarterly at Children's Healthcare of Atlanta. These Coordinators' Forums provide learning opportunities on a variety of research-related topics to the Coordinators. Information on Forum topics and schedules may be obtained through the Clinical Research department.

Introduction to Clinical Research classes are offered during the year at Children's Healthcare of Atlanta. These classes provide a broad overview of the research process including the history of research, protocol development, budgeting, compliance and the protection of human subjects. Anyone interested in research and the research process is invited to attend. More information can be found by accessing the ASPEN learning system through Careforce Connection.

5.3 PROFESSIONAL RESEARCH ASSOCIATIONS

Several professional research associations exist to provide continuing education, training, and research certifications for clinical research professionals. Some of these associations include:

Association of Clinical Research Professionals (ACRP)

Purpose. The mission is to "Provide global leadership to promote professional excellence for the clinical research profession." ACRP is the premiere organization for clinical research professionals in the pharmaceutical, biotechnology, and medical device industries, as well as those in hospital, academic medical centers, and physician office settings worldwide. Founded in 1976, ACRP is comprised of a diverse network of clinical research professionals including clinical research coordinators, investigators, and associates, research and development project managers, regulatory affairs and compliance professionals, and quality control and assurance auditors. ACRP membership spans 64 countries and includes 20,000 members and 59 global chapters.

Details. *Persons eligible:* Membership is open to all professionals engaged in clinical research. Annual meetings: Global Conference and Exhibition, European Conference and Exhibition. Publications: *The Monitor* (bimonthly peer-reviewed periodical), *Wire* (monthly e-newsletter). ACRP has two affiliate organizations: The Academy of Pharmaceutical Physicians and Investigators (APPI) and The Academy of Clinical Research Professionals. APPI is a physician-only membership. The Academy houses certification and government relations.

Contact. U.S.: ACRP Global Headquarters, 500 Montgomery Street, Suite 800, Alexandria, VA 22314-1581, 703-254-8100, fax 703-254-8101, Web site: www.acrpnnet.org Atlanta chapter: acrpatlanta.org

Society of Clinical Research Associates (SoCRA)

Purpose. As an international nonprofit membership organization SoCRA: encourages all clinical researchers including professionals working at investigational sites, in academia, in industry and in government to improve and develop their capabilities in subject areas beneficial to the medical and research community and the community at-large; enhances recognition by the medical community of the professionalism of the clinical researcher; offers opportunities for peer-to-peer recognition, understanding and information exchange; establishes training programs and continuing education programs for persons involved in or interested in clinical medical research, including consistent educational programming such as a regularly scheduled annual conference and other courses, workshops and seminars related to clinical science and clinical trials, and applicable regulations and international guidelines; nurtures regional educational activities through an established network of chapters; and supports an internationally recognized certification program (Certified Clinical Research Professional [CCRP]) for all professionals involved in clinical research.

Details. *Persons eligible:* All persons interested in clinical research. Annual meetings. *Publications:* *The SoCRA SOURCE* (quarterly magazine).

Contact. SoCRA Office, 530 West Butler Avenue, Suite 109, Chalfont, PA 18914-3209, 800-762-7292 or 215-822-8644, fax 215-822-8633, Web site: www.socra.org Georgia Chapter: gasocrainfo@yahoo.com

6.0 **Grant Writing**

- 6.1 Types of Grants
- 6.2 Components
- 6.3 Grant Revisions

A grant is an amount of money, given by a foundation, corporation, government or other type of organization to fund a project. Grants can provide support for a portion or an entire project and can include both direct and indirect costs. The purpose of writing a grant is to ask a funding source to give you money for your project.

The following has been Excerpted from "The Art of Grantsmanship" by Jacob Kraicer, M.D., Ph.D.

Before you begin writing—Read the guidebooks, guidelines and application forms carefully and follow them exactly. Make sure that you have the latest versions.

- *Make sure that your proposal fits with the mission of the agency and that your objectives match with those of the agency. Make this match explicit in your written application.*
- *If you have any doubts or questions, contact the relevant granting agency person, who will welcome your questions and answer them.*

- Find out the median funding level for the agency. This will allow you to formulate a reasonable budget.
- Find colleagues who have served on, or have received grants from, the agency. They can give you information on how the agency works.

Begin to formulate/clarify your ideas.

- Do you have a clear, concise and testable hypothesis?
- Are your objectives and aims coming into focus?
- What questions are to be addressed?
- Can you define and design specific experiments that will directly test your hypothesis?

Put together and write your recent work and submit it to appropriate peer-reviewed journal(s). Do this well in advance so that the work can appear in your application as published, in press or as a submitted manuscript. Most granting agencies will not accept a manuscript in preparation. Your track record, as judged by publications, is an important criterion in the assessment.

Carry out appropriate preliminary (pilot) studies, so that their results can be included in the application. This is especially important for new applications. It will also establish for you, and for the reviewers, whether the experimental approaches are feasible and which may be potential pitfalls.

Find and study previous grant proposals of successful colleagues. Consider these as models.

Find out, if you can, who are the members of the review committee and focus accordingly.

Identify essential and appropriate investigators who wish to collaborate with you. Discuss ideas with colleagues in the same and relevant fields. Going through the process of explanation and discussion will help to clarify and focus your ideas, and to identify possible gaps in logic.

A comprehensive guide, *The Art of Grantsmanship*, can be found at: <http://www.physpharm.fmd.uwo.ca/undergrad/survivalwebv3/ArtofGrantsmanship.html> .

Successful Grant Writing: Strategies for Health and Human Service Professionals by Laura N. Gitlin and Kevin J. Lyons is helpful book for with effective strategies and work models for grant writers.

Access <http://grants.nih.gov> for information about the NIH grants process.

6.1 TYPES OF GRANTS

Types of grants:

- A. Local—Emory—Emory Egleston Children’s Research Center (EECRC), Friends Research Fund, Dudley Moore Research Fund, Health Systems Institute (HSI) seed grants
- B. Regional: American Hospital Association Southeast affiliate
- C. National: American Heart Association, American Lung Association, Muscular Dystrophy Association, American Cancer Society, etc.
- D. National Institutes of Health (NIH)
 - a. Institutional Research Training grants—T32
 - b. K awards (mentored research awards)—K08 Mentored Clinical Scientist Development Award and K23 Mentored Patient-oriented Research Career Development Award.
<http://grants2.nih.gov/training/careerdevelopmentawards.htm>
 - c. Research Project Grant Program—NIH RO1 (individual research award)—these must be supported by substantial amounts of preliminary data. These are five-year renewable awards. For an example see: <http://www.niaid.nih.gov/ncn/grants/app/default.htm>
For application forms see: <http://grants.nih.gov/grants/funding/phs398/phs398.html>
 - d. Small Grant Program—NIH RO3—limited in time and budget and is not renewable. It is used to initiate a new research program to generate preliminary data. It is a step toward further support.
 - e. Exploratory/Developmental Research Grant Award—R21—also not renewable, but allows more time than the RO3. It has the purpose of supporting high-risk or high-impact research. It is a step toward further support.
 - f. NIH program grant—or request for application (RFA) or request for response (RFR) format—uses above forms. See <http://grants.gov/>

The Center for Scientific Review (CSR) is responsible for most of the grant applications submitted to NIH and oversees the peer-review process for them. <http://cms.csr.nih.gov/>

Funding Sources:

The Grantsmanship Center: <http://www.tgci.com>

Grants.Gov: www.grants.gov

National Science Foundation: www.nsf.gov/

National Institutes of Health: <http://grants.nih.gov/grants/index.cfm>

U.S. Department of Health and Human Services: www.hhs.gov/grants

<https://www.nih.gov>

6.2 COMPONENTS

It generally takes three to six months to write a grant application, and approximately another nine months from submission to funding.

Visit www.nsf.gov/pubs/2004/nsf04016/nsf04016.pdf for tips from the National Science Foundation

Visit www.fdncenter.org/getstarted/tutorials/shortcourse/info.html for tips from the Foundation Center.

Timelines

www.research.umich.edu/proposals/PWG/pwgdeadlines.html:

First, start with the sponsor's guidelines. Mark them as you study, noting such things as deadline (mailing or arrival), number of copies, where to mail, etc. As more grants have electronic submissions, note the time zone to make the deadline. The guidelines will also probably specify certain topics or questions that must be addressed. If you can reasonably say anything at all on these topics, you should use the sponsor's exact phrases as your headings. You may even wish to borrow some of the language of the guidelines if it fits naturally into the framework of your proposal. If the sponsor is looking for transdisciplinary approaches to the problem, you would do well to use that term rather than say, interdisciplinary or interdepartmental to describe the same activities.

Second, after you have studied the guidelines, if there are sections that are either too vague or too specific for comfort or convenience, check with the project representative to see if she has a clarification. If she does not, she may call the appropriate program officer at the agency for you or give you the number of the person to call. In either event, two ends will be served: the project representative will be alerted to your intentions to submit, and the information you will receive will help focus further the task of preparing a rush proposal.

Third, break the proposal up into small and simple subsections—especially if more than one person will be writing. Give each subsection headings and subheadings (referring again to the guidelines), and write meticulously to this outline. Using subheadings liberally will not only help you to organize your material, but it will also guide reviewers through your narrative. For facilitating last-minute corrections in the typed copy, start new sections and major subsections on new pages, and don't number pages, except lightly in pencil, until the last step.

Fourth, compare your budget and your text to ensure that for every cost figure a corresponding activity is mentioned and justified in the text.

Fifth, pay special attention to the abstract. Having rushed through the narrative, you will find that careful construction of the abstract will serve both as a summary of what you intend to do and as a check on whether you have omitted any essential topics.

The grant should include specifics sections:

TABLE OF CONTENTS

- Introduction
- Planning Your Application
- Abstract
- Research Plan (overview)
 - Specific Aims
 - Background and Significance
 - Preliminary Results/Progress Report
 - Research Design and Methods
- Budget and Justification
- Assurances
 - Human
 - Animal

INTRODUCTION

Some proposals require an introduction, in which you establish your organization's credibility as a funding recipient. This section may include:

- Background information on your organization, including its establishment and its history
- Unique characteristics of your organization.
- Significant accomplishments of your organization.
- Organizational goals.
- Support received from other organizations.

This introduction should be brief, avoiding jargon and tangential information.

NIH—PLANNING YOUR APPLICATION

Several key issues should be considered before, during and after your application is written.

- The usual deadlines for new NIH grant applications are: Feb. 1, June 1 and Oct. 1.
- The usual deadlines for amended applications and competing renewal applications are: March 1, July 1 and Nov. 1.
- **Please note:** The deadlines for investigator-initiated applications related to AIDS and in response to RFAs may differ.
- The review and selection process for applications takes eight to 10 months.
- Before you begin writing your grant application, read the PHS 398 instructions carefully and become familiar with all the requirements and certifications necessary. If you are submitting, in response to a published initiative such as Program Announcements (PA) or Request for Applications (RFA), read the PA or RFA in detail. If at all possible, find someone in your institution that can assist you in understanding and completing the application. Ask your colleagues for copies of successful NIH grant applications to get a more concrete idea of what each section should include. Incomplete applications are returned without review. Visit www.niaid.nih.gov/ncn/grants/app/default.htm for an example.
- Establish deadlines for the preparation of the grant application, particularly when collaborating investigators are involved. Be aware of

institutional deadlines that could delay your application. Allow time for equipment failures, personnel shortages, etc.

- Reread your application. Have someone else read it. Proofread it again.
 - If several people are contributing to the writing, decide who will do the final editing.
 - If possible, have objective experts (e.g., successful grantees, an institutional panel) review your proposal. Friends or close associates are rarely as critical as the reviewers on an NIH study section.
 - Do not feel inhibited about requesting technical assistance from the funding agency or your institution. Talk to the program representative who will manage the grant for advice on scientific and technical issues, and to the grants management specialist for advice on administrative issues. Your institutional grants office can also be of assistance. Talk to them and find out how they can help you.
 - Investigate any special research priorities of funding agencies, and ascertain from the program representative whether your project falls within the scope of an existing initiative (RFA or PA) or an area of special emphasis.
 - When submitting a revised application, answer all reviewer concerns mentioned in the earlier Summary Statement. Changes you make in the revised application must be described and illustrated, e.g., bracketing, underlining, etc. Regardless of how you feel, do not insult the reviewers. If you differ in your opinion try to courteously convince the reviewers of your point of views. In addition to responding to specific reviewer concerns, review all other aspects of the application to determine whether updating or improvement is necessary or possible.
 - **First Award Applicants:** letters of reference and institutional commitment are very important, particularly the wording or phrasing of these letters. You should emphasize this to those who will write your letters. The institutional commitment letter, in particular, should clearly state that the applicant has independent lab space and adequate equipment. Any other tangible expression of institutional commitment that might exist (start-up funds, support for a technician, etc.) should be mentioned. This indicates to Study Section members that you are not merely a worker but have independence and institutional support.
-

ABSTRACT

Purpose: The purpose of the abstract is to describe succinctly every major aspect of the proposed project except the budget. The abstract is an important part of your application. It is used in the grant referral process along with a few other parts of the application, to determine what study section is appropriate to review the application and

to what institute at NIH it is most relevant. Members of the Study Section who are not primary reviewers may rely heavily on the abstract to understand your proposal.

Recommended Length: The recommended length of the abstract will vary among different funding agencies, but the NIH abstract is a half-page, and confined to the designated space provided in the application.

Content

The abstract should include:

- A brief background of the project
- Specific aims or hypotheses
- The unique features of the project
- The methodology (action steps)
- Expected results
- Evaluation methods
- Description of how your results will affect other research areas
- The significance of the proposed research

Suggestions

- Be complete, but brief.
 - Use all the space allotted.
 - View the abstract as your one-page advertisement.
 - Write the abstract last so that it reflects the entire proposal. Spend time reviewing it.
 - Remember that the abstract will have a longer shelf life than the rest of the proposal and may be used for purposes other than the review, such as to provide a brief description of the grant in annual reports, presentations or in response to requests from top management at NIH.
-

RESEARCH PLAN (Overview)

Purpose: The purpose of the research plan is to describe the *what*, *why* and *how* of the proposal. This is the core of the proposal and will be reviewed with particular care. The *what* will be Part A: Specific Aims; the *why*, Part B: Background and Significance; and the *how*, Part C: Preliminary Results contributes to both the *why* and *how*. Part D: Research Design and Methods. The assessment of this research plan will largely determine whether or not the proposal is favorably recommended for funding.

Recommended Length: The maximum length of the research plan is 25 pages.

Content: The research plan should answer the following questions:

- What do you intend to do?
- Why is this worth doing? How is it innovative?
- What has already been done in general, and what have other researchers done in this field? Use appropriate references. What will this new work add to the field of knowledge?
- What have you (and your collaborators) done to establish the feasibility of what you are proposing to do?
- How will the research be accomplished? Who? What? When? Where? Why?

Suggestions

- Make sure that all sections (A, B, C and D—the *what*, *why* and *how* of the proposal) are internally consistent and that they dovetail with each other. Use a numbering system, and make sections easy to find. Lead the reviewers through your research plan. One person should revise and edit the final draft.
 - Show knowledge of recent literature and explain how the proposed research will further what is already known.
 - Emphasize how some combination of a novel hypothesis, important preliminary data, a new experimental system and/or a new experimental approach will enable important progress.
 - Establish credibility of the proposed principal investigator and the collaborating researchers.
-

RESEARCH PLAN PART A: Specific Aims

Purpose: The purpose of the specific aims is to describe concisely and realistically what the proposed research is intended to accomplish.

Recommended Length: The recommended length of the specific aims is one page.

Content: The specific aims should cover:

- Broad, long-term goals
- The hypothesis or hypotheses for testing
- Specific time-phased research objectives

Suggestions:

- Generally, the Specific Aims section should begin with a brief narrative describing the long-term goals of the project and the hypothesis guiding the research. This is followed by a numbered list of the Aims.
 - **State the hypothesis clearly.** Make sure it is understandable, testable and adequately supported by citations in the Background and by data in the Preliminary Results Sections. Be sure to explain how the results obtained will be used to test the hypothesis.
 - Show that the objectives are attainable within the stated time frame.
 - *Be as brief and specific as possible* for clarity. Each aim should consist of only one sentence. Use a brief paragraph under each aim if detail is needed. Most successful applications have two to four specific aims.
 - Be certain that all aims are related. Have someone read them for clarity and cohesiveness.
 - Focus on aims where you have good supporting preliminary data and scientific expertise.
-

RESEARCH PLAN PART B: Background and Significance

Purpose: The purpose of the background and significance section is to state the problem to be investigated, the rationale for the proposed research, the current state of knowledge relevant to the proposal and the potential contribution of this research to the problem(s) addressed.

Recommended Length: Approximately three pages

Content: The background and significance section should cover:

- The rationale for the proposed project
- The state of existing knowledge, including literature citations and highlights of relevant data
- Gaps that the project is intended to fill

Suggestions

- Make a compelling case for your proposed research project. Why is the topic important? Why are the specific research questions important? How are the researchers qualified to address these questions?
 - Establish familiarity with recent research findings. Avoid outdated research. Use citations not only as support for specific statements but also to establish familiarity with all of the relevant publications and points of view. Your application may be reviewed by someone working in your field. If their contributions and point of view are not mentioned, they are not likely to review your application approvingly.
 - Make sure the citations are specifically related to the proposed research. Cite and paraphrase correctly and constructively.
 - Highlight why research findings are important beyond the confines of a specific project i.e., how can the results be applied to further research in this field or related areas.
 - Stress any innovations in experimental methods (e.g., new strategies, research methods used, interventions proposed).
-

RESEARCH PLAN PART C: Preliminary Results/Progress Report

Purpose: The purpose of the preliminary results section is to describe prior work by the investigators relevant to the proposed project. In a new application, the preliminary results are important to establish the experience and capabilities of the applicant investigators in the area of proposed research and to provide experimental support for the hypothesis and the research design. This section is not mandatory for new applications, but it is virtually impossible to obtain a favorable review without strong preliminary data. In a competing renewal application, this section becomes a progress report describing studies performed during the last grant period.

Recommended Length: The recommended length of the preliminary results/progress report section is six to eight pages.

Content: The preliminary results section should include the following:

- Most importantly, a description of recent studies by the applicant investigators that establish the feasibility and importance of the proposed project.
- A brief description of older published studies by the applicant that provide important background information relevant to the proposed project.
- Results of previous studies by the applicant not directly relevant to the proposed project if they are needed to establish the applicant's competence and experience with the experimental techniques for the proposed project.

Suggestions

- All Tables and Figures necessary for the presentation of preliminary results must be included in this section of the application. Full-size glossy photographs of materials such as electron micrographs, gels, etc., may be included in the appendix, but only if a photocopy (reduced in size, as appropriate) is included in the body of the Research Plan.
 - Figures and Figure legends must be legible. There are specific limits on type size given in the application instructions, but beyond these rules, the critical factor is whether the data are legible and convincing to the reviewers.
 - Do not dwell on results already published. Summarize the critical findings in the text and include reprints of the full article in the appendix. Up to 10 publications can be included with the appendix material.
-

RESEARCH PLAN PART D: Research Design and Methods

Purpose: The purpose of the research design and methods section is to describe how the research will be carried out. This section is crucial to how favorably an application is reviewed.

Recommended Length: The maximum recommended length of the research design and methods section is 20 pages.

Content: The research design and methods section should include the following:

- An overview of the experimental design
- A detailed description of specific methods to be employed to accomplish the specific aims
- A detailed discussion of the way in which the results will be collected, analyzed and interpreted
- A projected sequence or timetable (work plan)
- A description of any new methodology used and why it represents an improvement compared to the existing ones
- A discussion of potential difficulties and limitations and how these will be overcome or mitigated
- Expected results, and alternative approaches that will be used if unexpected results are found
- Precautions to be exercised with respect to any procedures, situations or materials that may be hazardous to personnel or human subjects.

Suggestions

Number the sections in this part of the application to correspond to the numbers of the Specific Aims.

- Give sufficient detail. Do not assume that the reviewers will know how you intend to proceed.
- Avoid excessive experimental detail by referring to publications that describe the methods to be employed. Publications cited should be by the applicants, if at all possible. Citing someone else's publication establishes that you know what method to use, but citing your own (or that of a collaborator) establishes that the applicant personnel are experienced with the necessary techniques.

- If relevant, explain why one approach or method will be used in preference to others. This establishes that the alternatives were not simply overlooked. Give not only the how but the why.
 - If employing a complex technology for the first time, take extra care to demonstrate familiarity with the experimental details and potential pitfalls. Add a co-investigator or consultant experienced with the technology, if necessary.
 - Document proposed collaborations and offers of materials or reagents of restricted availability with letters from the individuals involved.
-

BUDGET AND JUSTIFICATION

Purpose: The purpose of the budget and justification is to present and justify all expenses required to achieve project aims and objectives. For multi-institutional applications, there must be a separate budget for each subcontractor or consortium member.

Recommended Length: Special forms are provided for the budget and justification. Read the instructions carefully. If there are other co-investigators at another institution, for whom funds are requested, be sure to include their budget.

Content: The budget and justification should cover the following:

- Personnel
- Consultants
- Equipment
- Supplies
- Patient care costs
- Lab, pharmacy, support services
- Travel
- Other expenses, e.g., animal maintenance

Suggestions:

- Be realistic. Both padding and deliberately budgeting less than you need reflects naiveté, which is often recognized by reviewers.
- Provide brief descriptions of duties for all positions listed in the budget, with the percentage of effort requested each year and any anticipated fluctuations. Special skills or accomplishments of a designated person may be included if not discussed elsewhere.
- If possible, try to identify specific individuals for each position requested. To be named personnel are very often deleted by reviewers.
- Justify all equipment purchases. The proposed acquisition of major pieces of equipment is likely to be scrutinized very carefully. Details are important, especially for nonproject specific equipment e.g., FAX machine and computers.
- Breakout supply costs into major categories (reagents, disposables, etc.). Provide special justification for any unusual expenses requested.
- Detail and justify travel costs. Make sure they reflect current fares and lodging costs, and that proposed travel is project-related.
- Explain any year-to-year fluctuations in the budget, including the level of effort of personnel, especially if they can not be attributed to routine salary increases. Changes should parallel the research plan and project aims.
- Check indirect costs. Some institutions have on-campus and off-campus rates.

- Be complete but concise. There are no page limits in this section.
 - Provide adequate justification for the need to use outside consultants, if applicable.
 - The budget must be approved by the grantee institution business office before they can sign the application.
 - If applicable, provide documentation of institutional rates for animal maintenance and acquisition. Exceptionally large numbers of animals will need detailed justification.
 - Prorate service contracts to percentage of time equipment is used for this project.
-

ASSURANCES

Purpose: The purpose of the assurances section is to ensure that the applicant organization will comply with all relevant federal laws and guidelines.

Recommended Length: A special form must be completed for the assurances section. See page B of the PHS 398 application.

Content: The assurances cover:

- Human subjects
- Vertebrate animals
- Inventions and patents
- Debarment and suspension
- Drug-free workplace
- Lobbying
- Delinquent federal debt
- Misconduct in science
- Civil rights
- Handicapped individuals
- Sex discrimination
- Age discrimination

Suggestions

- Be familiar with assurances, certifications and requirements for complying with these regulations.
 - Begin to obtain assurances early, because they tend to require the cooperation of different institutions.
 - Check your institution's grants management office for additional requirements. Different institutions follow different procedures and timelines.
-

HUMAN SUBJECTS

Purpose: The purpose of this section describing the involvement of human subjects is to ensure the protection of the rights and welfare of people who participate in research projects.

Recommended Length: There is no specified length, but be succinct.

Content: Provide a complete description of the proposed involvement of human subjects as it relates to the work outlined in the Research Plan section. If an exemption has been designated in item 4a on the face page, enough detail still must be provided to allow the

determination of the appropriateness of the exemption. If no exemption is claimed, there are six points which must be addressed in this section. A full description of these points can be found on page 22 of the PHS 398 application package. Be thorough in addressing these six areas.

All research applications involving human subjects **must** address the issue of inclusion of women and minorities in the subject population. A justification is required if there is limited representation of women and minorities. Peer review and NIH program staff will consider this justification in their evaluation of your application.

The assurance of compliance number from the NIH Office of Protection from Research Risks (OPRR) must be provided in item 4b of the face page, as must the IRB approval date.

Suggestions

- Most institutions have a multiple project assurance from OPRR. If your institution does not, contact OPRR as soon as possible to obtain a single project assurance.
 - All research involving human subjects requires a current review by your IRB. Be sure to provide the most recent review date for your project.
 - You must provide information on the inclusion of women and minorities in the study population.
-

VERTEBRATE ANIMALS

Purpose: The purpose of this section describing the use of vertebrate animals is to ensure the humane treatment of live animals involved in the proposed research.

Recommended Length: There is no specified length, but be succinct.

Content: Provide a complete description of the proposed use of vertebrate animals as it relates to the work outlined in the Research Plan section. There are five points which must be addressed in this section. A full description of these points can be found on page 23 of the PHS 398 application package. Be thorough in addressing these five areas. Failure to address any of these areas will delay any award until these issues have been resolved.

The animal welfare assurance number from the NIH Office of Protection from Research Risks (OPRR) must be provided in item 5b of the face page, as must the Institutional Animal Care and Use Committee (IACUC) approval date.

Suggestions

- Most institutions have a multiple project assurance from OPRR. If your institution does not, contact OPRR as soon as possible to obtain a single project assurance.
 - All research involving vertebrate animals requires a review by your IACUC. Be sure to provide the most recent review date for your project.
 - Be sure the number of animals proposed is realistic.
 - Justify all animal expenses.
-

RESOURCES AND ENVIRONMENT

Purpose: The purpose of the resources and environment section is to describe the resources, facilities and support available to the researcher.

Recommended Length: A special form is provided for the resources and environment section.

Suggestions

- Make sure the resources and environment section addresses all requirements of the proposed research plan.
 - Justify any reliance on resources external to the research.
 - Make sure all subcontractors and consortium members have the capability to perform the tasks assigned to them.
 - Make certain your resources and budget requests are consistent.
-

OVERALL CONSIDERATIONS

- Observe application guidelines strictly.
- Use basic English and avoid jargon.
- Make sure all acronyms are spelled out when used initially.
- Type single-spaced and stay within the margins.
- Observe the type size and page limitations strictly; do not use a small font.
- Do not use photo reductions on a copy machine, particularly gels, etc., because they may become unreadable.
- Draw or print all graphs, diagrams, charts and tables in black ink (be consistent with formats). Label these items carefully.
- Include only those graphs, tables, etc., that are essential to the narrative; these should complement the text and be appropriately inserted.
- List all citations (six pages maximum) at the end of the research plan.
- Make sure all citations are complete: title, authors, book or journal, volume number, inclusive pages, year of publication.
- Have an outside reader review the proposal for clarity and consistency.
- Proofread carefully by reading aloud. Do not rely on computer spell check to find mistakes.
- Be consistent with terms, references and form writing style.
- Supplement the text material by including additional information in the appendices. However, appendices should contain supportive or supplemental, rather than essential material. Essential data should be included within the body of the application. Provide a table of contents of the appendices for easy reference by the reviewers.
- Make sure the application is signed and dated by you (the Principal Investigator) and by the designated institutional business official.
- Make sure all the check-box items on page II of the PHS 398 application are completed.
- Be sure that your application is received at the Division of Research Grants by the appropriate deadline.

6.3 GRANT REVISIONS

The usual deadlines for amended NIH applications and competing renewal applications are: March 1, July 1 and Nov. 1.

When submitting a revised application, answer all reviewer concerns mentioned in the Summary Statement. Changes you make in the revised application must be described and illustrated, e.g., bracketing, underlining, etc. Regardless of how you feel, do not insult the reviewers. If you differ in your opinion try to courteously convince the reviewers of your point of views. In addition to responding to specific reviewer concerns, review all other aspects of the application to determine whether updating or improvement is necessary or possible.

Visit www.nlm.nih.gov/ep/FAQRevise.html for information about revising an unsuccessful grant application.

7.0 Research Methods and Statistical Design

- 7.1 Basic Elements of Study Design
- 7.2 Basic Types of Study Design
- 7.3 A General Guide to Statistical Consultation
- 7.4 Basic Statistical Terms

Proper research method design and statistical design/analysis are crucial in clinical trials. Research methodology will impact the planning, conduction and outcomes of the clinical trial.

7.1 BASIC ELEMENTS OF STUDY DESIGN

The structure of a research project is outlined in its protocol; the written plan of the study. Protocols have a vital scientific function: helping the investigator to organize his/her research in a logical, focused and efficient way. Elements of the study design include the following:

- **Research Questions (Objectives)**
The research question is the objective of the study, the uncertainty of a health issue that the investigator wants to solve. Research questions often begin with a vague and general concern that must be focused to a concrete, researchable issue.
- **Significance (Background)**
The significance section of a protocol sets the proposed study in context and gives its rationale. What is known about the topic, why the research is important, and what kinds of answers the study will provide. This section cites previous research that is relevant, including the investigator's own work, and indicates the problems with that research and what questions remain. It makes clear how the findings of the proposed study will help resolve these uncertainties and influence clinical practices.

- **Design**
The design of a study is a complex topic that involves a number of decisions. Basic types of study design is explained in further detail below (Section 7.2) Timeframe and approach are some main areas around which study design decisions should consider.
- **Subjects**
There are two major decisions to be made in choosing study subjects:
 1. Selection Criteria—the process of defining the study population: What kinds of patients are best suited for the research study and where would you recruit them?
 2. Feasibility of Selection Criteria—the process of determining the feasibility of recruitment in the current environment. Is it realistic to recruit for a study involving Alaskan Inuit children in Georgia?

- **Variables**
Another major decision in designing a study concerns the choice of which characteristics of the study subjects, to measure. In a descriptive study the investigator looks at the individual variables one at a time. In an analytic study the investigator analyzes the relationship among two or more variables in order to predict outcomes and to draw inferences about cause and effect.

In considering the association between two variables, the variables involved are:

1. Predictor Variables—the preceding variable that is presumably the cause.
2. Outcome Variables—the following variable that is presumably the effect.

- **Statistical Issues**
The investigator must develop plans for the managing and analysis of study data. For analytic studies and experiments, this always includes a hypothesis-testing component: specifying in advance at least one main hypothesis (a version of the research question that has the purpose of providing the basis for testing the statistical significance of the findings).

Some other statistical considerations are:

1. Sample Size Estimation—estimating the number of subjects needed to consistently observe the expected difference in outcome.
2. Analytic Approach—the statistical tests to be used in answering the study questions.

7.2 BASIC TYPES OF STUDY DESIGN

The most fundamental decision to consider in designing a study is whether the study will stand apart from the events taking place in the study subjects (**observational study**) or to test the effects of an intervention on these events (**experimental study**). If the investigator chooses an observational design, his/her next decision is whether to make the measurements on a single occasion (**cross-sectional study**) or during a period of time (**longitudinal study**). A third aspect if the design decision is whether to deal exclusively with past events (**retrospective study**) or to follow subjects for events that have not yet occurred (**prospective study**).

- **Single Center versus Multicenter Trials**

Single center trials are done in one institution. The primary rationale for multicenter trials relates to recruitment. It may not be possible to recruit a sufficient number of patients at one site to afford statistical significance. A multicenter (and multi-investigator) trial also provides a better basis for the subsequent generalization of its findings, reduces single center biases and populations, etc.

Participation of more than one center is logistically more complicated. It necessitates ensuring that the protocol is appropriate for all centers, exclusion/inclusion criteria are agreed (where standardization of disease criteria may not be agreed internationally), that there are no language problems, that rating scales are used consistently and so forth. Nevertheless, with an efficient coordinating center and appropriate training, multicenter trials can be most effective.

- **Qualitative versus Quantitative**

Research may be described as quantitative or qualitative research. Qualitative research is the non-numerical examination and interpretation of observations, for the purpose of discovering underlying meanings and patterns of relationships. In addition, quantitative research is the numerical representation and manipulation of observations for the purpose of describing and explaining the phenomena that those observations reflect. Quantitative and qualitative research has certain differences. Quantitative research utilizes deductive reasoning to determine a hypothesis. It involves numbers and statistics to infer to a general sample. Typically, a causal relationship is explored with controlled conditions. Qualitative research utilizes inductive reasoning and observation to develop a hypothesis or research question. Open-ended questioning and analysis take place looking for processes that explain why or how something occurred. Narrative descriptions and themes usually evolve as data. Comparison is used to understand and enlighten the specific population being studied and cannot typically be generalized to a larger population.

- **Controlled, Uncontrolled and Historically Controlled Trials**

Controlled trials are designed to compare two treatments (active group versus control group).

One of three types of control group can be used:

1. **Placebo Group**—Many controlled trials utilize a placebo group, where the placebo is a pharmacologically inactive compound, formulated/packaged in such a way as to be indistinguishable from the active treatment.
2. **Different Dosage**—Different dosages of the same medicinal therapy can also be compared in a controlled trial.
3. **Standard Therapy or Standard of Care**—In other trials the control group is “standard therapy or standard of care”, i.e. the best currently available treatment.

The disadvantages of controlled trials are their inflexible and restricted natures, and that they bear little resemblance to clinical practice. However, without controlled trials no efficacious medicine would reach the target population.

Uncontrolled trials do not include any comparator. Generally these are restricted to exploratory trials such as the estimation of dosages for subsequent studies. However, such general practice trials are also uncontrolled.

Historical controls—On rare occasions results from clinical trials are compared with so-called historical controls, i.e.: patients treated with the new therapy are compared with patients from previous trials who received the standard therapy. Such comparisons should be avoided, if possible, because it is virtually impossible to ensure that the historical controls are matched in every way with the treatment group in the present trial.

- **Avoidance of Bias**

Randomization—Bias must be excluded from a clinical trial to avoid influencing the results. Randomization is performed to avoid such bias, and to ensure that each patient has an equal chance of receiving either treatment. Randomization is an effective means of reducing bias in treatment selection because it guarantees that treatment assignment will not be based on the patient's prognostic factors. Note that randomization should only be carried out after the patient has been included in the trial.

Stratification—Stratification involves the random allocation of treatments to different classes of patients. Common stratification criteria are gender, age and severity of disease. Stratification and intention to evaluate stratified groups at trial onset affords deliberate subgroup analysis after the trial, rather than artificial data massage to try to get a significant result.

Blinding—Blinding is the process by which investigators mask the subject's treatment/placebo group. There is a need to know when unblinding is permissible/required, i.e.: if a serious adverse event occurs and the identity of the treatment is vital for patient care.

- **Parallel-group versus Crossover Trials**

Parallel-group trials—In parallel-group trials, each group receives only one treatment for the whole duration of the trial

Crossover trials—In crossover trials, each group receives both treatments. Confounding factors with crossover studies include the necessity of incorporating a wash-out phase to ensure that treatment effects from the first part of the trial do not affect responses in the second part, and prolongation of the trial compared with a parallel-group trial because both groups need to receive each treatment for the same length of time. For example, a patient in group number one will receive treatment one for three months, followed by three months wash-out period, followed by three months treatment two. And a patient in group number two will receive treatment two for three months, followed by three months wash-out period, followed by three months of treatment one.

7.3 A GENERAL GUIDE TO STATISTICAL CONSULTATION

Statistical consultation should be done in parallel with the study design due to the importance of outcomes as a result of statistical issues. Along with assistance in study design, statistical consultation also offers the following on analysis of data:

- **Intent-to-treat and Per-protocol Analyses**

Factors to consider in study data include patient withdrawal, patient noncompliance, and patients not attending follow-up or incomplete data entry. There may be a seemingly legitimate rationale for omitting such patients from data analysis. However, to do so will compromise the randomization procedure and render subsequent statistical analysis potentially flawed.

An intent-to-treat analysis is an analysis of all patients randomized to receive treatment. The per-protocol analysis includes only patients who fulfilled all the protocol requirements throughout the entire trial. Normally, both analyses are performed and compared.

- **Interim Analysis**

Interim analysis is undertaken before termination of a trial and should be described in the protocol/amendment. Such an analysis should only be conducted for strictly scientific reasons, such as perceived greatly enhanced or reduced efficacy in one of the treatment arms of the trial.

- **Subgroup Analysis**

Any subgroup analysis should be predetermined (i.e.: based on stratification procedures) such that the trial is designed to detect significant differences between the specified subgroups. Posthoc subgroup analysis, however, although potentially useful in designing new trials, should not be viewed as providing significant statistical data.

- **Meta-analysis**

Meta-analysis is an attempt to analyze data from a number of similar studies. Meta-analysis may give some beneficial results, especially in terms of highlighting relatively rare events or where treatment effects are not pronounced. The principal problems with meta-analysis are that, in general, trials demonstrating positive results are more likely to be published than those with negative results (thus skewing any analysis), that protocols are seldom identical (i.e.: endpoint definition) and that the design of the trials is likely to be heterogeneous in terms of the methodology and statistical power.

7.4 BASIC STATISTICAL TERMS

Analysis of Covariance—a statistical technique to control for the correlation between a subject variable and a dependent variable in an experiment. This procedure removes the error variance that results from the fact that variability in scores on the dependent variable is due in part to the effect of the subject variable.

Analysis of Variance (F Test)—a statistical significance test for determining whether two or more means are significantly different. F is the ratio of systematic variance to error variance.

Chi-square Test—a statistical significance test used when dealing with nominal scale data. It is used when the data consists of frequencies

Correlation Coefficient—an index of how strongly two variables are related to each other in a group of subjects.

Degrees of Freedom (df)—a concept used in tests of statistical significance; the number of observations that are free to vary to produce a known outcome.

Error Variance—random variability in a set of scores that is not the result of the independent variable. Statistically, the variability of each score from its group mean.

Mean—a measure of central tendency, obtained by summing scores and then dividing the sum by the number of scores.

Median—a measure of central tendency; the middle score in a distribution of scores that divides the distribution in half.

Mode—a measure of central tendency; the most frequent score in a distribution of scores.

Standard Deviation—the average deviation of scores from the mean (the square root of the variance).

Systematic Variance—variability in a set of scores that is the result of the independent variables; statistically, the variability of each group mean from the grand mean of all subjects.

t-test—a statistical test most commonly used to examine whether two groups are significantly different from each other. The t value is a ratio of two aspects of the data, the difference between the group means and the variability within the groups.

Type I Error—an incorrect decision to reject the null hypothesis when it is true.

Type II Error—an incorrect decision to accept the null hypothesis when it is false.

Validity—the extent to which a measurement instrument measures what it is intended to measure.

Variability—the amount of dispersion of scores about some central value.

Variance—a measure of the variability of scores about a mean; the mean of the sum of squared deviations of scores from the group mean.

8.0 Protocol Design/Review

8.1 Elements of a Study Protocol

- 8.2 IRB Review
 - 8.3 Study Flowchart
-

The study protocol is the detailed plan of the study. The study protocol should be written after the planning is complete. Every research study should have a protocol.

The written protocol:

- Forces the investigators to clarify their thoughts and to think about all aspects of the study.
- Is a necessary guide if a team (not a single investigator) is working on the research.
- Is essential if the study involves research on human or animal subjects, in order to get the institution's ethical approval.
- Is an essential component of a research proposal submitted for funding.

During the process of the development of the protocol, investigators can, and should, try to benefit from the advice of colleagues and experts in refining their plans. But once a protocol for the study has been developed and approved, and the study has started and progressed, it should be adhered to strictly and should not be changed. This is particularly important in multicenter studies. Violations of the protocol can discredit the whole study. If the violations are minor, at least that part of the study should be excluded from the analysis.

A well-thought and well-written protocol can be judged according to three main criteria.

1. Is it adequate to answer the research question(s), and achieve the study objective?
2. Is it feasible in the particular set-up for the study?
3. Does it provide enough detail that can allow another investigator to do the study and arrive at comparable conclusions?

The protocol should outline the rationale for the study, its objective, the methodology used and how the data will be managed and analyzed. It should highlight how ethical issues have been considered, and where appropriate, how gender issues are being addressed. (A Practical Guide for Health Researchers, WHO 2004, chapter 5, pgs 65-71. www.emro.who.int/dsaf/dsa237.pdf)

8.1 ELEMENTS OF A STUDY PROTOCOL

Items to be included in a protocol (or associated documents) for research involving human subjects:

- Title of Study
- Study Personnel
- Background and Purpose
- Summary of Procedures
- Risks
- Potential Benefits
- Inclusion and Exclusion Criteria
- Informed Consent/Assent Process

- Lay Summary (optional)
- Study Population
- Data Handling and Analysis
- Control of Investigational Product (Drug or Device)

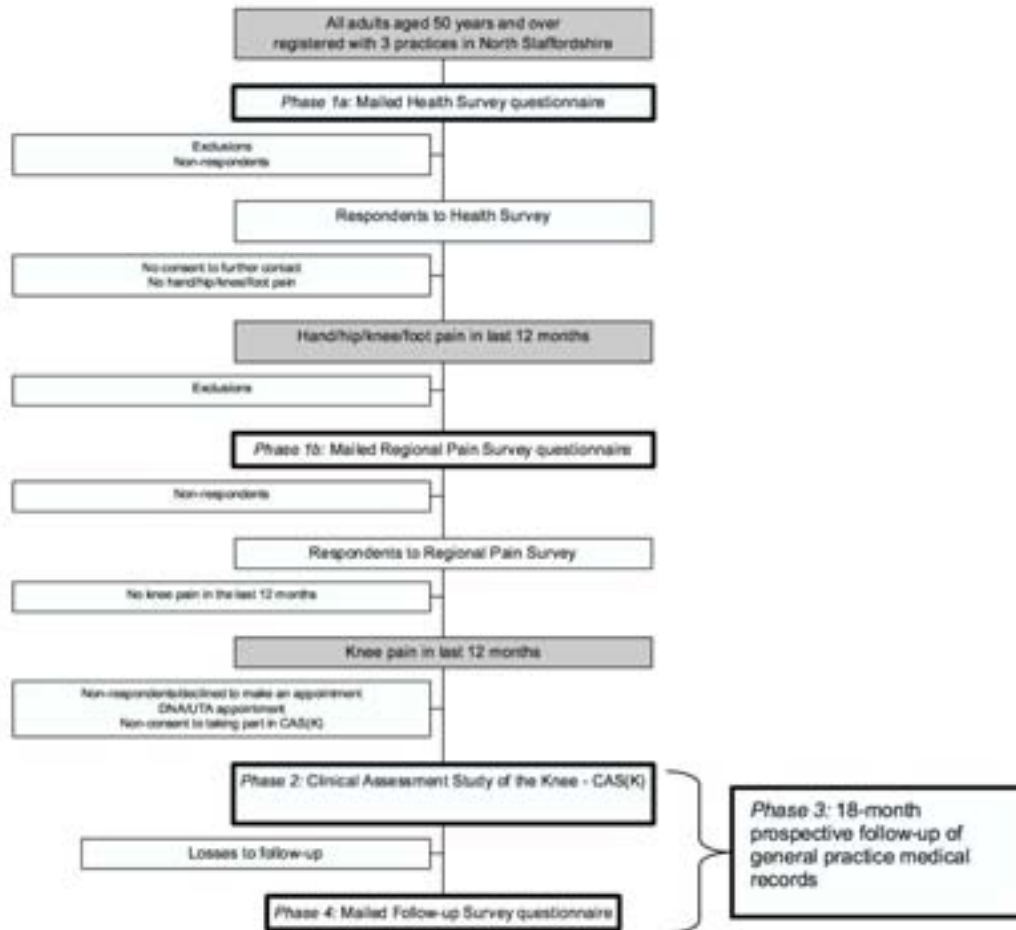
8.2 IRB REVIEW

- A. In order to approve a protocol the IRB shall determine that the following requirements are satisfied as appropriate to the protocol:
1. The risks to the subjects are minimized.
 2. The risks to the subjects are reasonable in relationship to anticipated benefits and the importance of the knowledge that may reasonably be expected to result.
 3. The selection of subjects is equitable.
 4. A process has been established for obtaining informed consent from each prospective subject or the subject's legal representative, in accordance with and to the extent required by DHHS and FDA regulations and the policies of the hospital.
 5. A process has been established to document informed consent.
 6. A procedure has been established to monitor the data collected to ensure the safety of subjects.
 7. The investigational research plan adequately provides for the protection of privacy of subjects and the maintenance of confidentiality of data concerning those subjects.
 8. Those applicable regulations for the protection of children (45 CFR 46, Subpart D) are satisfied.
- B. The IRB may take into consideration, in its review of the proposed research, any prior approvals or disapprovals by other institutional review boards at other institutions. The IRB however is in no way bound by these approvals or disapprovals.

8.3 STUDY FLOWCHART

Flowcharts are helpful in showing the sequential order of all study procedures and decision points. This is a visual way of depicting your research to reviewers.

Below is an example—(Peat et al. BMC Musculoskeletal Disorders 2004 5:4 doi:10.1186/1471-2474-5-4, Figure 1.)



Data collection points are in bold

www.biomedcentral.com/1471-2474/5/4/figure/F1

9.0 Research Involving Drugs and Devices

- 9.1 Investigational Drug Studies
- 9.2 Investigational Device Studies
- 9.3 Investigator's Brochure

9.1 INVESTIGATIONAL DRUG STUDIES

Investigational New Drug Application (IND)

- Research use of an unapproved investigational drug or biologic must be done with an IND application process through the FDA.

- Current federal law requires that a drug or biologic be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

Sponsor Responsibilities

- Sponsor-initiated protocols require the sponsor to file the IND application with the FDA.
- All FDA/sponsor IND correspondence must be submitted to the IRB with the research application.

Investigator Responsibilities

- Investigator-initiated protocols require the PI to file an IND application with the FDA. The IND application and instructions are found at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
- The FDA IND application and all subsequent correspondence between the FDA and the investigator must be submitted to the IRB.
- Although FDA regulations permit research to begin 30 calendar days after the IND application has been filed, the IRB will make the final determination on a case-by-case basis to assure that research subjects will not be subject to unreasonable risk.

IND Waiver

An IND waiver applies to the clinical investigation of a drug product that is lawfully marketed in the United States. In order to be exempt from the requirement for an IND, the investigator must apply for a waiver to the IRB advising that all of the following conditions have been met. As part of the protocol review, the IRB will determine the appropriateness of the waiver.

- The investigation is not intended to be reported to the 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.

Treatment Use of an Investigational Drug

The FDA permits an investigational drug to be used for treatment use with a treatment protocol or treatment IND when:

- The drug is intended to treat a serious or life-threatening disease.

- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population.
- The drug is under investigation in a controlled clinical trial with an IND in effect for the trial, or all clinical trials have been completed.
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

Treatment protocols require review and approval by the IRB.

- } See the Children's policy 1.55—Investigational Drugs, Biologics and Dietary Supplements in Research and policy 1.60—Emergency Use of Investigational Drugs, Biological Products and Devices for additional information.
<http://careforce/cms/default.aspx?id=2057>

9.2 INVESTIGATIONAL DEVICE STUDIES

Definition

A medical device is defined, in part, as any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized. Medical devices also include diagnostic aids, such as reagents and test kits for *in vitro* diagnosis.

Investigational Device Exemption (IDE)

1. An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21CFR part 812].
2. Unless exempt from the IDE regulations, an investigational device must be categorized as either significant risk (SR) or nonsignificant risk (NSR).
3. SR studies require submission to the FDA for an IDE. The FDA IDE application and all subsequent correspondence between the FDA and the sponsor/investigator must be submitted to the IRB.
 - IDE application and instructions are found at <http://www.fda.gov/cdrh/devadvice/ide/print/application.html>
4. NSR studies require the usual IRB review and approval with regard to informed consent, record keeping and study monitoring.
5. Device studies require review and approval by the IRB.
6. If an investigator proposes the initiation of a claimed NSR investigation to the IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin immediately, without submission of an IDE application to FDA.
7. Any safety and efficacy data collection on an SR device for other than approved indication requires an IDE in advance of IRB approval.

- } See the Children’s policy 1.56—Investigational Devices for additional information—located in the Policy Section of this manual and on the Clinical Research site on Careforce Connection. <http://careforce/cms/default.aspx?id=2057>

SR and NSR Definitions

1. An SR device study is defined as a study of a device that:
 - Presents a potential for serious risk to the health, safety, or welfare of a subject and
 - Is intended as an implant; or
 - Is used in supporting or sustaining human life; or
 - Is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
 - Otherwise presents a potential for serious risk to the health, safety of welfare of a subject.
2. An NSR device investigation is one that does not meet the definition for a significant risk study.
3. Visit <http://www.fda.gov/oc/ohrt/irbs/devices.html#risk> for examples of SR and NSR devices.

9.3 INVESTIGATOR’S BROCHURE

Research protocols developed by industry often involve development and testing of INDs. The proposal developed by an industry sponsor to test an investigational agent will include a protocol and an Investigator’s Brochure. FDA regulations [21 CFR 312.23 (5)] state that an Investigator’s Brochure must contain the following information:

1. A brief description of the drug substance and the formulation.
2. A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
3. A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
4. A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies.
5. A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and or precautions or special monitoring to be done as part of the investigational use of the drug.

Applications for IRB approval must include a copy of the most current Investigator’s Brochure from the sponsor.

The content of the Investigator’s Brochure may change during the course of the study, and the sponsor will issue a new brochure to investigators. Sponsors expect investigators to submit the revised brochures to the IRB as they are issued. The IRBs require submission of the revised brochure with a cover letter to explain any changes

and a revised consent form(s) to reflect updated information. The IRB will review any recommended changes in the study based on new information and communicate the outcome of the review to the PI.

10.0 Research Involving Human Tissue

- 10.1 Tissue Repository at Children's
- 10.2 Tissue Bank at Emory

10.1 TISSUE REPOSITORY AT CHILDREN'S

Guidelines for storing tissues in the Pathology ultra low temp freezer are similar to the requirements guiding the handling and storage of diagnostic surgical pathology specimens.

- Personal Protective Equipment (PPEs) must be worn at all times when handling tissue samples with universal precautions being adhered to as well.
- Vials containing tissue must be labeled prior to placement in to the freezer. The way in which these vials are labeled is based upon how the tissue samples will be used in the future.
 - If the tissue is to be used for future diagnostic tests, the vial should be labeled with the patient's name, surgical pathology accession number and tissue type.
 - If the tissue is being placed in to the freezer as part of the biorepository, the vial should be labeled with the deidentifier number generated by the repository database. The vial(s) should not be labeled with any information that will link the tissue to a specific patient.
 - All vials stored should be logged into the repository database or freezer logbook. It is poor management to allow items to be stored in the freezer without tracking their contents, reason for storing and storage requirements. Therefore, only items that have been approved for storage by Pathology and/or the Biorepository committee will be stored in Pathology freezers.
- For tissue samples that RNA or DNA analysis is to be performed on in the future, it is advisable to snap freeze the vial(s) of tissue immediately following collection just prior to placement in the freezer. It is important to note that tissue vials cannot be stored in liquid nitrogen as the materials they are constructed of are not stable enough for this process.
- When storing tissue samples in an ultra low-temp freezer, a contingency plan must be in place to address incidents of freezer failure. To ensure the integrity of the samples, this plan must be initiated as soon as possible after the freezer fails.
 - At Children's at Egleston, a contingency plan will be initiated when the freezer temperature reaches or exceeds -60° C. At this time, samples will be packed on dry ice and transported to the Emory Tumor Bank for temporary storage until the freezer is repaired.

- At Children's at Scottish Rite, a contingency plan will be initiated when the freezer temperature reaches or exceeds -60° C. At this time, samples will be transported to the back-up ultra low-temp freezer, which is located in the Children's at Scottish Rite morgue, until the freezer is repaired.

} For more information see the Children's policy 1.62—Use of Human Biological Materials in Research. <http://careforce/cms/default.aspx?id=2057>

10.2 TISSUE BANK AT EMORY

The Emory Human Tissue Procurement and Banking Service (HTPBS) is a core facility whose purpose is to collect, distribute and bank human tissues to support the research of clinicians and scientists in Emory University. It is sponsored by the School of Medicine with strong support from the Winship Cancer Institute. The HTPBS is located physically within Emory University Hospital and is supervised by the Department of Pathology and Laboratory Medicine assisted by a multidisciplinary Advisory Board appointed by the Associate Dean of Research. The Advisory Board, chaired by the Medical Director of the HTPBS, will interface with the Emory IRB to validate IRB approval and with the Dean's Office regarding resource allocation. The committee will approve and modify procedures for the HTPBS such as what tissues are procured and how they are prioritized for distribution. It will ensure appropriate standards are met for establishment of satellite banks and it will engage in long-term strategic planning.

Sources of tissue for the HTPBS are the hospitals within the Emory Healthcare system (Emory University Hospital, Crawford Long Hospital, Grady Memorial Hospital and Veterans Administration Hospital). Procured tissues are surgical and autopsy tissues that are not used for diagnostic purposes. The tissues supplied may be fresh, formalin and alcohol-fixed paraffin blocks, and OCT-embedded tissue-types suitable for a variety of experimental approaches. An online searchable database allows registered users to query the availability of specific banked organs or tissue-types by various parameters (e.g. pathologic diagnosis, clinical stage, patient demographic, processing methods). Biopsy samples associated with a clinical trial protocol are collected and/or archived for specific investigators by special arrangement.

The HTPBS facilitates the fresh or immediate need tissue requests of investigators, in addition to coordinating the prospective tissue acquisition, processing and distribution for programmatic or organ-specific satellite banks. The satellite banks are maintained and funded by HIC-approved investigators or programs. Tissue will be provided to as many requesting investigators as possible. Requests may be made for samples with specific characteristics or parameters, e.g. grade and stage, gene expression or lab result ranges, etc.

11.0 Monitoring Plan Development

- 11.1 Roles
 - 11.2 Scope
 - 11.3 Timing
-

The purpose of the data safety monitoring plan is to assure that clinical research subjects are not exposed to unnecessary or unreasonable risks and that the investigator conducts the clinical trial according to the highest scientific and ethical standards by providing data safety monitoring plans for all clinical trials.

For each proposed clinical trial, Children's requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks, size and complexity of the clinical trial.

A detailed data and safety monitoring plan must be submitted to the IRB for approval prior to the accrual of human subjects. The NIH and other funding agencies requires the establishment of a Data and Safety Monitoring Board (DSMB) for multisite clinical trials involving interventions that entail potential risk to the participants, and generally for phase III clinical trials.

- } See the Children's policy 1.57—Data and Safety Monitoring of Clinical Research Studies for additional information. <http://careforce/cms/default.aspx?id=2057>

11.1 ROLES

1. Principal Investigator (PI) will determine, based on risk, whether a board, committee or individual will be monitoring the study. The PI or the sponsor will write the plan.
2. Data Safety Monitoring Committee (DSMC)—the monitoring committee set up internally, or within the system, to monitor a study. DSMCs typically meet every six months.
3. Data Safety Monitoring Board (DSMB)—the monitoring board set up externally, usually by the study sponsor, to monitor a study. DSMBs typically meet every six months.
4. Institutional Review Board (IRB)—The IRB is responsible for reviewing and approving the monitoring plan.

11.2 SCOPE

When the PI is developing the plan, it is important to determine the monitoring scope of the plan. Elements of a monitoring plan are:

1. Define the authority of the monitoring individual(s) with regard to advising or making recommendations concerning continuation, revision or discontinuation of the research project.
2. Include the process for making such recommendations or decisions.
3. Include the specific procedures that will be used to monitor for and report adverse events, protocol violations and deviations.
4. Include timing and frequency of data analysis.
5. Include periodic assessment of the following:
 - a. Participant recruitment and retention, to assure the feasibility of meeting recruitment projections.
 - b. Data quality and timeliness.

- c. Participant risk versus benefit, taking into consideration the impact of new scientific or therapeutic developments.
- d. Study site performance.
- e. The procedure and schedule for timely reporting to sponsors and the IRB.

11.3 TIMING

The Principal Investigator must include in the plan, a procedure and schedule for timely reporting to the IRB and sponsors, if applicable, as well as timing and frequency of data analysis.

12.0 *Case Report Form Development*

- 12.1 Content, Organization and Format
- 12.2 Tips for Creation
- 12.3 Electronic Data Capture

A Case Report Form (CRF) is a printed or electronic document designed to record all of the clinical protocol required information to be reported on each clinical trial subject. The CRF can be created for the Sponsor or an Investigator-initiated study.

A trial protocol specifies what information from subjects' case histories will be recorded for analyses. The required information is collected on CRFs. There is a set of CRFs for each trial subject. The data derived is from source documents such as the medical record or research records created to collect data.

The Sponsor/Investigator designs and provides the CRFs to the trial sites. Prior to initiating a trial, the staff responsible for completing the CRFs must understand what is required for every line in each CRF: the rationale for the collecting the data, the timing of data collection, the consequences of not collecting the data properly, the format to be used in entering the data on the CRF, and how and when the completed CRFs are to be sent to the Sponsor.

NOTE: Most CRFs are printed. However, there are clinical trials in which the CRFs are electronic; the data is entered directly into a computer.

The PI must ensure the completeness, accuracy, legibility and timeliness of the clinical data entered on CRFs. Data derived from source documents are to be consistent with the source documents; any discrepancies must be explained. Additionally, some sponsors may require that the Investigator for the study sign-off on the final CRFs, attesting to the accuracy of the data being submitted.

All corrections to CRFs are to be dated, initialed and explained (if necessary). The correction should be a single line through the incorrect information, making sure that it is still legible. Only authorized investigative site staff may make CRF entries and/or corrections. Sponsors should have written procedures to assure that changes or

corrections in CRFs are communicated to the Sponsor. The Sponsor and the Investigator should retain records of the changes and corrections.

12.1 CONTENT, ORGANIZATION AND FORMAT

When determining content consider the following:

- The content is based on what the PI wants to achieve from the protocol
- The end points
- The parameters
- The demographics

Examples of Case Report Forms are:

- Subject Information—includes patient demographic data
- Adverse Event Forms—details adverse events
- Study Procedures Check-off List
- Concomitant Medications—list of medicines patient is taking
- Delegation of Duties—list of staff working on a trial with corresponding trial-related duties
- Enrollment Log
- Inclusion/Exclusion Criteria
- Medical History
- Nonenrollment Log—why was patient not enrolled
- Operative Data—collection of interoperative data
- Parental Intake Data—data collected from parents
- Physical Exam
- Progress Notes

Before the study:

- Test a draft of the CRF by using data from existing patient records to complete the form.
- Determine with the monitor the procedures for completing the CRFs, as well as how and when to send CRFs from your site to the data entry point.
- Ensure that all study staff authorized to complete the CRF are familiar with the procedures. This delegation must be documented and authorized staff must complete the delegation/signature list.
- Make sure you know the procedure for assigning patient identification. The patients name must never be entered onto the CRF.
- Discuss with the monitor whether some of the data (protocol-specific data) in the CRF should be considered source data. Make sure that these are specified.

During the study:

- The monitor will ensure that you are completing the CRF without error or omission, and that your entries are legible.
- Make sure, well in advance of seeing a patient, that you have all the necessary documentation.
- Cross out any incorrect entries on the CRF with a single line so that the original entry is still legible underneath.

- Initial and date any correction made; if not immediately obvious, explain why the correction was necessary.
- Do not leave any part of the CRF blank as the data analysts will not know how to interpret this. Instead, describe why data have not been provided, for example write, not done or not applicable.
- Sign-off the CRF to indicate its completeness and accuracy.
- Ensure that all documentation is available and up to date before each site visit by the monitor.
- Continually send data from the site to the data entry point following a time schedule agreed upon with the monitor, or according to other agreed procedures. This will enable reporting soon after completion of the trial.

After the study:

- Retain your copy of the CRFs for the time period agreed upon with the monitor.

} See the Children’s Standard Operating Procedure—Handling Monitoring Visits for more information—Appendix P

SOURCE DOCUMENT FORMAT

Source documents should be designed with specific protocol in order to capture all necessary information for the study (i.e.: demographics, endpoints and safety data). Source document format, therefore, should be set up to appropriately follow GCPs in capturing both pertinent study-related information per protocol, as well as other clinical information that is important to the subjects' overall care. Source documents should provide a global view of the subjects' care, with specific information and details that can be used to satisfy study data requirements. In this sense, source documents should not mirror CRFs only.

12.2 TIPS FOR CREATION

The following tips may be helpful in creating CRFs:

- The main goal of data collection is to collect specific data to meet the research objectives of the protocol. All data collected should support the objectives of the protocol.
- Fields should capture data required by protocol including demographics, safety information, inclusion/exclusion criteria, any adverse events and follow-up visits.
- Keep questions and instructions clear and concise.
- The flow of the CRF should follow study procedures or the anticipated organization of data in the medical record.
- Avoid redundant data points.
- Aside from measurements, which will have to be entered, create checkboxes by providing multiple choices where possible. This will limit entry error.

12.3 ELECTRONIC DATA CAPTURE (EDC)

EDC is a computerized system for collecting data from clinical trials of new drugs or devices using electronic case report forms instead of paper (eCRF vs. CRF).

EDC Process:

- Site coordinators complete source docs
- Monitoring visits are still required, although fewer may be necessary
- Coordinators and monitors still perform source document verification
- CRFs still exist, although in electronic format

Possible Data to be Imported:

- Laboratory Data
- Interactive Response Voice System (IVRS)
- Patient Diary
- Images
- Device/Monitor Readouts
- Drug Inventory/Clinical Supplies

EDC Site Advantages:

- Data is entered in the eCRFs during or immediately after a patient visit.
- Edit checks (e.g., range checks) are built into the eCRFs which eliminates many typo and common errors.
- Study staffs can remotely review and query eCRFs.
- Sites receive and resolve queries shortly after patient visit while the information is still recent and memorable.
- At the conclusion of the study, eCRFs are generally stored on a CD which reduces sites' storage issues

13.0 *Informed Consent Form Development*

- 13.1 General Writing Tips
 - 13.2 Elements of Informed Consent
 - 13.3 Informed Consent Template
 - 13.4 Assent
-

13.1 GENERAL WRITING TIPS

When writing an informed consent, remember that the consent process is to provide enough information to the potential subjects to allow him/her to make an informed decision of whether or not to participate in the study. Protecting the subjects' right is also extremely important. The consent should detail how their rights are going to be protected if they choose to be in the study.

Tips to Consider:

- Do not hesitate to use the words volunteer and placebo.

- Be certain that the statement of benefits are not self-serving, i.e., written so as to induce the prospective subject to participate.
- State clearly any compensation or cost (compensation for time and travel).
- Present possible alternative therapies; it is not sufficient to say the investigator will discuss alternatives or that there are no alternatives.
- Define medical/technical concepts in simple lay language, e.g., randomization needs to be described in language such as flip of a coin.
- Be sure to include the statement that the subject is to be given a copy of the consent form.
- Try to write the consent at an eighth grade language level.
 - In Microsoft Word, click on *Tools*, then *Options*
 - Select the *Spelling & Grammar* tab
 - Check the *Show readability statistics*
 - Then, click *OK*
 - Press the F7 key
 - After the spelling and grammar check is complete, it will give you the *Readability Statistics*
 - In the *Readability* section, the grade level will be listed

To make the consent form more readable:

1. Write short sentences and short paragraphs.
2. Use simple words and phrases, e.g., use not utilize; use not that involve the use of.
3. Use simple declarative sentences. Avoid the passive voice. The language in an informed consent form should be readily understood by someone who has not graduated from high school.
4. Format the document using:
 - Large type
 - Subheadings
 - Ample white space
5. Use page numbers.
6. Proofread the document carefully and focus on:
 - Typographical, grammatical, spelling and usage errors.
 - The consistent use of first or second person.

Simplifying Informed Consent Forms

Complex	Simpler	Easy
additional	Extra	more
administer	Dispense	give
adverse	Negative	bad; harmful
appropriate	Suitable	proper; right
approximately	Nearly	about

Complex	Simpler	Easy
available	Present	handy
categories	Classes	groups
combination	Series	mix
compensation	Payment	money
consequences	Outcomes	results
empirical evidence	Studies	research
equivalent	Equal	same
immediately	at once	now
initiate	Begin	start
medications	Medicines	drugs

13.2 ELEMENTS OF INFORMED CONSENT

1. General Considerations: There are special circumstances in which the Children's IRB may decide that prospective informed consent is not required for a human subject research study. In all other cases, Investigators shall obtain informed consent using methods that provide prospective subjects and/or their legally authorized representatives sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information given to the subjects shall be in a language understandable to the subjects and/or their legally authorized representatives. No informed consent, oral or written, shall include any exculpatory language through which the subjects are made to waive, or appear to waive, any of their legal rights, including any release of the investigators, the sponsors, the institutions or their agents from liability for negligence.

The information provided to the subjects and/or their legally authorized representatives shall be written in language understandable to a layperson and shall include the following elements:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the subject's participation.
- A description of the research procedures to be followed.
- Identification of any procedures which are experimental.

- A description of any reasonably foreseeable risks or discomfort to the subject and the precautions that will be taken to minimize those risks.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and the possibility that the FDA or the Office of Human Research Protections (OHRP) may inspect such records.
- An explanation as to whether any compensation for participation will be provided and whether any medical treatment will be available if injury occurs. If medical treatment will be available, the subject shall be advised as to what it consists of or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury.
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, the following information shall also be provided to the subjects and/or their legally authorized representatives:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is, or may become, pregnant) which are unforeseeable.
- Anticipated circumstances where the subject's participation may be terminated by the investigator without his or her consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject on a timely basis.
- The approximate number of subjects involved in the study.

An informed consent form shall be developed for each research study unless the IRB determines that a waiver of written informed consent is appropriate. The informed consent form shall contain all information necessary to ensure that the subject is properly informed and protected as required by the FDA, OHRP and the Children's IRB. The original signed informed consent form will become a permanent part of the subject's research record at the study site and a copy will be placed in the subject's medical record at Children's.

} See the Children's Standard Operating Procedure —Informed Consent Submission, Revision, and Approval for additional information—located in the Appendix Section of this manual (Appendix B).

- } For non-English speaking patients see the Children's policy 1.64—Oral Interpretation for Limited English Speaking (LES) Persons and Written Translation of Consent Forms for Research. <http://careforce/cms/default.aspx?id=2057>

13.3 INFORMED CONSENT TEMPLATE

- } Currently Children's requires that this standard informed consent template is used for all research purposes. This standard template can be found on the Clinical Research Web site within the Institutional Review Board, Forms and Instructions section <http://careforce/cms/default.aspx?id=687> and in Appendix C of this manual.

13.4 ASSENT

When children or minors are involved in research the regulations require the assent/consent of the child and the permission of the parent(s) or legal guardian(s).

The requirement for parental or guardian permission may be inappropriate in some cases. Examples include research involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (e.g., treatment for venereal disease, drug abuse or emotional disorders).

Permission is not necessary when the research involves the observations of public behavior when the investigator(s) do not participate in the activities being observed.

Given that children have not reached their full intellectual and emotional capacities, involving children in research requires the permission of their parents or legally authorized representatives (unless parents and representatives are designated to be legally incompetent). The IRB must determine whether the permission of both parents is necessary, and the conditions under which one parent may be considered not reasonably available.

While children may be *legally* incapable of giving informed consent, they nevertheless may possess the ability to assent/consent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. Thus, adequate provisions should be made for soliciting the assent/consent of the children when, in the judgment of the IRB, the children are capable of providing such assent/consent.

- } See the Children's policy 1.61—Assent and Legally Authorized Representative Permission in Pediatric Research for additional information—located on the Clinical Research site on Careforce Connection. <http://careforce/cms/default.aspx?id=2057>

14.0 Health Insurance Portability and Accountability Act (HIPAA) Authorization

- 14.1 Overview
 - 14.2 HIPAA Authorization Form
 - 14.3 IRB Exemption/Waiver of HIPAA Authorization
-

14.1 OVERVIEW

HIPAA is a federal patient privacy law that specifies requirements for accessing subject/Protected Health Information (PHI).

HIPAA became effective on April 14, 2001
Compliance required by April 2003

Part of HIPAA requires:

1. Improved efficiency in healthcare delivery by standardizing electronic data interchange.
2. Protection of confidentiality and security of health data through setting and enforcing standards.

HIPAA is enforced by U.S. Department of Health and Human Service (HHS). The HHS has implemented the Privacy Rule. One purpose of the Privacy Rule is the protection of individuals PHI. The Privacy Rule protects all individually identifiable health information held or transmitted in any form or media, whether electronic, paper or oral. PHI includes identifiers such as name, address, birth date and Social Security number.

The Children's HIPAA Policy Regarding the Use and Disclosure of PHI for Research Purposes and the Role of the Institutional Review Board (IRB) as well as all other HIPAA-related policies at Children's can be found on Careforce Connection under policies and procedures.

Request for use or disclosure of PHI for research purposes must be reviewed and approved by the IRB. The IRB will determine whether the use or disclosure requires authorization by the research participant or whether the use or disclosure may be made pursuant to an alteration or waiver, in whole or in part, of the authorization requirement with HIPAA. The IRB will only grant a full or partial HIPAA waiver if the waiver criteria are satisfied.

14.2 HIPAA AUTHORIZATION FORM

- } The Children's Authorization to Release Protected Health Information for Research Purposes form can be obtained by visiting the IRB section on the Clinical Research Web site and clicking on Forms & Instructions
<http://careforce/cms/default.aspx?id=687>

14.3 IRB EXEMPTION/WAIVER OF HIPAA AUTHORIZATION

A covered entity may use or disclose information for research purposes without the written authorization of the research subject if the covered entity receives written documentation that waiver of authorization has been approved by the IRB.

Criteria for the IRB to Grant a Waiver of Authorization

The IRB must determine that the following criteria are met in order to grant a waiver of authorization:

- (a) Minimal Risk—The use or disclosure of the PHI presents no more than a minimal risk to the privacy of the subject based on the presence of at least the following criteria:
 - (i) Protection Plan—An adequate plan to protect identifiers for the PHI from disclosure or improper use.
 - (ii) Destruction Plan—An adequate plan to destroy the identifiers at the earliest possible opportunity consistent with the conduct of the research, unless there is a health, research or legal justification for maintaining the identifiers.
 - (iii) Assurance Against Redisclosure—Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research or for other research for which the use or disclosure of the PHI would be permitted by HIPAA.
- (b) Need for Waiver—The research could not practicably be conducted without the waiver or alteration of the authorization.
- (c) Need for PHI—The research could not practicably be conducted without access to, and use of, the PHI.
- (d) No Adverse Effects—The grant of the waiver will not adversely affect the rights or welfare of the research subject [required by current IRB regulations].

Context in Which This Means of Access Should Be Used

Studies requesting a waiver of informed consent in order to conduct the study: If an investigator is requesting a waiver of informed consent and the study involves the use of PHI, that investigator is also required to request a waiver of authorization. The IRB will make two determinations that are similar but use different criteria. Investigators will be required to submit information addressing all criteria.

Subject Recruitment—Although patient authorization is the preferred method or obtaining access to PHI, authorization may be impractical or impossible to obtain in the subject recruitment setting. The healthcare providers in the covered entity may discuss with their patients the possibility of enrolling in a research protocol as follows:

- (a) The patient's physician may recruit the individual for an IRB-approved research protocol (both therapeutic and nontherapeutic), but must obtain the subject's Authorization for disclosure of PHI for research purposes even if the

patient's physician is also the researcher

(b) A researcher seeking to recruit patients must either ask a covered provider to make the contact with the prospective subject or seek an IRB waiver of authorization to obtain the individual's contact information. The IRB can waive authorization for this purpose, even if the research protocol requires the individual's authorization to participate. In most cases, the primary care provider of the potential research subject will be the preferred advocate for the subject's interests and will be the preferred contact point for communications with the subject concerning recruitment for research studies.

- } See the Children's policy 8.15—Uses and Disclosures for Research Purposes & Waivers (HIPAA Research Policy) for additional information—located on the Clinical Research site on Careforce Connection. <http://careforce/cms/default.aspx?id=2057>
- } For further HIPAA Information see Appendix D—The National Institutes of Health HIPAA Privacy Rule Information for Researchers.

15.0 Subject Recruitment Plan

- 15.1 Considerations for Subject Payments
- 15.2 Privacy Rules Regarding Subject Recruitment
- 15.3 Clinical Trials Web Posting

FACTORS TO CONSIDER IN RECRUITING SUBJECTS

The inclusion/exclusion criteria—The designer of the clinical trial might have defined a somewhat theoretical patient, one that is ideal for the design of the study, but impractical in terms of finding such patients. For example, recruiting diabetics might sound easy for an endocrinologist, but if the inclusion/exclusion criteria are very narrow with respect to age, history of diabetes and prior treatment, there might be few patients who meet the criteria. In recruiting trial subjects, the recruiter must take into consideration what type of advertising makes sense given the inclusion/exclusion criteria.

The number of trial-related visits—If there are frequent visits, or a large number of procedures, the likelihood of recruiting a sufficient number of subjects may decrease, and the probability of subjects dropping out of the trial may increase.

Resources for recruiting—Depending upon the nature of the trial, many contacts may be required to find and recruit subjects. A good plan must be developed with adequate resources for successful recruitment.

The marketing message—Your advertising message targeted to prospective trial subjects must be very clear. You do not want to draw the interest of those who are unqualified for the trial. A response to advertising from a subject who has no likelihood of qualifying for the trial slows the recruiting process and wastes time and money. Even more importantly, the message must be accurate, straightforward and noncoercive.

NOTE: Be certain that advertising materials have been approved by the sponsor and the IRB, and that planned searches of any patient records meet HIPAA regulations. In

general, authorization or an IRB waiver of the authorization requirement is required before screening medical records for research purposes.

- } See the Standard Operating Procedure Advertising for Study Subject Recruitment for further information. (Appendix E)

Competing trials—If there are other clinical trials near your site that have similar inclusion/exclusion criteria, the available patient population for your trial is diminished.

The recruitment plan—Based on the above points, you should develop a recruitment plan which takes into account the eligibility criteria and the prevalence of the disease in the general public. For example, you might not be successful in advertising in a small community for a trial studying a rare cancer. It is important to plan the target audience, the geographic area, the message and what to do if your recruiting plan is not successful.

Legal and Ethical Issues Concerning Recruitment of Subjects

Recruiting subjects to participate in a clinical trial is a highly regulated activity, and the recruiter must take care to ensure that all ethical and legal issues are considered. Make sure that:

- Advertising is not misleading or coercive.
- Risks are disclosed to potential trial subjects.
- Any stipend or other incentive is not presumed coercion.
- Privacy rights of potential and enrolled subjects are protected.

To help ensure that all ethical and legal points are considered, you must submit to the IRB all scripts for verbal presentations, flyers, advertisements, posters, radio spots, brochures, etc., which are to be used to advertise a trial with the intent to recruit subjects. In addition, if video recruitment materials are to be used, the videos themselves must be submitted.

KEY POINTS

- No claims can be made, either explicitly or implicitly that the investigational agent (drug, biologic, or diagnostic) or device is safe or effective for the purposes under investigation, or that the investigational agent is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also violate FDA regulations.
- A phrase such as receive new treatment implies that all study subjects will be receiving newly marketed products of proven worth. Therefore, do not use terms such as new treatment, new medication or new drug without explaining that the investigational agent is investigational, and, if appropriate, that some subjects will receive standard treatment or placebo. Remember, federal regulatory authorities do not consider research to be treatment.
- If the IRB has approved stipends or other incentives for trial subjects, an advertisement may state that subjects will be compensated for their

participation, but should not emphasize the payment or state the amount to be paid. Advertisements should not promise free medical treatment when the intent is only to say subjects will not be charged for taking part in the investigation.

15.1 CONSIDERATIONS FOR SUBJECT PAYMENTS

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred by taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment (undue inducement). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

Acceptable Recompense—Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefit from the research may also receive a small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

Unacceptable Recompense—Monetary or in-kind payments to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; local ethical review committees may find such inducements acceptable. Monetary and in-kind recompense must, therefore, be evaluated in the light of the traditions of the particular culture and population in which they are offered, to determine whether they constitute undue influence.

Incompetent Persons—Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

Withdrawal From a Study—A subject who withdraws for any other reason should be paid in proportion to the amount of participation. An investigator who must remove a subject from the study for willful noncompliance is entitled to withhold part or all of the payment.

15.2 PRIVACY RULES REGARDING SUBJECT RECRUITMENT

Identifying Research Participants

The preparatory to research provision states that covered entities may use or disclose PHI to researchers to aid in study recruitment. The covered entity may allow a researcher, either within or outside the covered entity, to identify, but not contact, potential study participants under the preparatory to research provision. However, before permitting this activity, a covered entity must receive proper representation from the researcher. Under the preparatory to research provision, no PHI may leave the covered entity. Covered entities may permit researchers to review PHI in medical records or elsewhere to prepare a research protocol or for similar preparatory to research purposes. This review allows the researcher to determine, for example, whether a sufficient number or type of records exists to conduct the research. Importantly, the covered entity may not permit the researcher to remove any PHI from the covered entity.

To permit the researcher to conduct a review preparatory to research, the covered entity must receive from the researcher representations that:

- The use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the covered entity during the review.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Contacting Research Participants

The preparatory to research provision states that covered entities may use and disclose PHI to researchers to aid in study recruitment. They may allow a researcher to identify, but not contact, potential study participants. To contact potential study participants, a researcher may do so, without authorization from the individual, under the following circumstances:

If the researcher is a workforce member of a covered entity, the researcher may contact the potential study participant, as part of the covered entity's healthcare operations, for the purposes of seeking authorization. In addition, a covered healthcare provider may discuss treatment alternatives, which may include participating in a clinical trial, with the patient as part of the patient's treatment or the covered entity's healthcare operations. Alternatively, the covered entity may contract with a business associate—who may be a researcher—to assist in contacting individuals on behalf of the covered entity to obtain their authorizations.

If the covered entity obtains documentation that an IRB has partially waived the authorization requirement to disclose PHI to a researcher for recruitment purposes, the covered entity could disclose to the researcher that PHI necessary for the researcher to contact the individual.

15.3 CLINICAL TRIALS WEB POSTING

In 2006, Sen. Christopher Dodd, a democratic representative from Connecticut, introduced S. 470, the Fair Access to Clinical Trials (FACT) Act. The measure would require the FDA to expand the ClinicalTrials.gov database to create a

publicly accessible national data bank of information comprised of a clinical trial registry and a clinical trial results database. The database would include a clinical trial registry accessible to patients and healthcare practitioners seeking information related to ongoing clinical trials for serious or life-threatening diseases and conditions. Also required would be a database of all publicly and privately funded clinical trial results, regardless of outcome, which would be accessible to the scientific community, healthcare practitioners and members of the public. S. 470 would further require the FDA to make internal drug approval and safety reviews publicly available. The clinicaltrials.gov Web site would continue to be run by the NLM with assistance from the FDA. Provisions of the FACT Act would apply to clinical trials for drugs, biologics and medical devices, and would require all trials to be registered in the database in order to obtain approval from a U.S.IRB.

ClinicalTrials.gov—All prospective clinical trials involving human subjects should be registered in compliance with the requirements of the International Committee of Medical Journal Editors (ICMJE). ICMJE member journals will not consider publishing trial results unless the trial is registered. All clinical trials conducted at Children's will be registered at <http://www.clinicaltrials.gov/>.

Clinical Trial (ICJME Definition)

Any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase I trials), are exempt.

The investigator has three options for clinical trials registration:

- Individual—if the clinical trial takes place outside of the Children's facilities in a private practice office. Individual accounts may be registered without the assistance of Children's. Investigators registering trials may refer to the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/> for assistance.
 1. Children's (as an organization account)—if the Investigator is an employee at Children's or a member of the Children's medical staff.
 - a. Request the Children's Research Coordinator assigned to the study to complete registration or
 - b. If no Children's Research Coordinator is assigned to the study, contact the Children's Clinical Trials Registration Administrator for assistance.
 3. Emory University (as an organization account)—if the Investigator is an Emory faculty member

16.0 Institutional Review Board (IRB) Submission

- 16.1 The Children's IRB Review
- 16.2 Determining Review Type
- 16.3 Submission Requirements
- 16.4 IRB Post-review Actions

16.5 External Institutional Review

16.1 THE CHILDREN'S IRB REVIEW

The Children's IRB operates in compliance with hospital research policy(ies) and with the U.S. Code of Federal Regulations, Department of Health and Human Services (DHHS) Title 45 Part 46, entitled Protection of Human Subjects, as well as the Food and Drug Administration (FDA) Title 21, Part 50 and Title 21 Part 56. The IRB reports to the Children's Audit and Compliance Committee of the Board in conjunction with Children's Administration.

- } For more information regarding the IRB and its operations please see Institutional Review Board Standard Operating Procedures, the Children's Policy 1.16
<http://careforce/cms/default.aspx?id=2057>

The Children's IRB meets monthly to review research proposals to be conducted at Children's or otherwise involving Children's faculty, staff, facilities or property. Children's researchers must submit a complete application packet to the IRB office. Proposals requiring full Board review will be scheduled for the earliest available meeting.

The IRB Chair or Vice Chair or his/her designee will ultimately determine whether the research proposal meets the criteria necessary for full Board or expedited review.

It is important to note that incomplete submissions will not be processed.

The IRB office will contact the Principal Investigator and study contact person regarding any documentation that is missing, and that information must be received before the submission may be forwarded for IRB review. If the submission must be reviewed by the full Board and the missing documentation is not received prior to the deadline for that month's meeting, the submission will be placed on the next available meeting agenda after it is complete.

16.2 DETERMINING REVIEW TYPE

A. TYPES OF REVIEWS

FULL BOARD REVIEW:

1. The full Board must review submissions that involve more than minimal risks to participants.
2. To ensure review at the current month's meeting, the submission must be complete, must meet the guidelines provided by the IRB and must be received in the IRB office before the meeting deadline.
3. Depending on the nature of the submission, an investigator may be asked to attend the IRB meeting to be available to answer questions.
4. Submissions may be approved by the IRB pending reply to concerns or requests for clarifications or revisions to study documents. A letter is sent by e-mail to the Principal Investigator and study contact person detailing

the requested revisions. The investigators have 90 days in which to reply to IRB requests regarding new studies; if no reply is received, the study is withdrawn from consideration and the IRB study file closed. If a reply is received and the Board's requests were satisfactorily addressed, the submission will be approved and a written Notification of Approval will be sent to the Principal Investigator and study contact person as well as IRB stamped approved copies of any associated informed consent/assent documents, Authorization to Release Protected Health Information forms, and recruitment materials. The investigator cannot begin research activities described in the submission until she/he receives a written Notification of Approval from the IRB.

5. Only study documents that will be used for the study shall be submitted with your IRB submission for review and approval by the IRB. Once your documents have been approved and stamped, these are the only documents that shall be used during the duration of the study. The stamped approved documents may also be used to make copies for study enrollment.
6. The Children's IRB will determine how often continuing review for the study is required. Per federal regulations, IRB approval will not be issued for a period longer than one year. Some studies may be considered high risk and will need review at more frequent intervals. The duration of approval will be noted in the Notification of Approval.

EXPEDITED REVIEW:

1. Submissions qualifying for expedited review (i.e., review outside of a full Board meeting) are not subject to any submission deadlines.
2. Submissions meeting the criteria for expedited review as defined by the Federal Register will be reviewed by one or more members of the Children's IRB who has sufficient knowledge and expertise to evaluate the human subject protection issues presented by the research request.

• **EXEMPT STATUS:**

1. Some studies may be determined by the IRB to be exempt from further IRB review if they are found to meet the federal requirements for this status. Investigators may not self-exempt their studies; the IRB must make this determination upon review of a complete submission.
2. Submissions meeting the criteria for exempt status will be reviewed by one or more members of the Children's IRB who has sufficient knowledge and expertise to evaluate the human subject protection issues presented by the research request.

} See the Children's Standard Operating Procedure—Obtaining and Maintaining IRB Approval (Appendix F)

16.3 SUBMISSION REQUIREMENTS

- Application Form

- Use the appropriate type, either Initial Submission Form or Initial Request for Review of Existing Data or Specimens Form
 - Protocol Summary (follow IRB template)
 - Justification for Determination of Risk of Device, as applicable
 - Review Preparatory to Research Form or Decedent's Information Form, as applicable
 - Informed Consent/Assent Form(s) (follow IRB template; not applicable if applying for a waiver of informed consent/assent)
 - Authorization to Release Protected Health Information Form or Waiver of Authorization Form, as applicable
 - Recruitment Material(s) and Questionnaire(s), if any will be used
 - Protocol
- } See the Children's Standard Operating Procedure—Handling IRB Correspondence (Appendix G)

16.4 IRB POST-REVIEW ACTIONS

After a protocol is reviewed by the full Board, the IRB response will usually be sent to the study contact person and the Principal Investigator within 10 working days of the date of the IRB meeting. If a protocol is reviewed on an expedited basis, the IRB response will usually be sent to the study contact person and the Principal Investigator within 10 working days of the date of submission to the IRB office.

16.5 EXTERNAL INSTITUTIONAL REVIEW

Children's and Emory Research are affiliated through a deferral agreement. Research is either approved by the Children's IRB or the Emory IRB per the following criteria:

1. Emory may rely on the Children's IRB for review and continuing oversight of its human subject research where an (a) Emory employee is serving as the Principal Investigator, investigator or other study personnel and (b) the research activity is limited to a review of the Children's medical records.
2. Children's may rely on the Emory IRB for review and continuing oversight of its human subject research that is (a) conducted under the supervision of a Principal Investigator who is employed by Emory University and (b) not limited to the review of the Children's medical records.

Emory's IRB submission process is entirely electronic, through a Web-based program e-IRB. All printed materials pertaining to the request for review must be scanned prior to submission. Employees of non-Emory entities may obtain access to e-IRB through a sponsored account. Instructions for this process can be found on the IRB Web site at www.emory.edu/IRB. Deadline dates, review dates, forms and committee members can also be found at the IRB Web site.

It is important to note that there are multiple steps in initiating research with external entities. Contact the Clinical Trials Office at CTO@emory.edu for additional information at Emory University,

All other institution's faculty/staff must go through the Children's IRB for research to be conducted at Children's.

17.0 Other Children's Reviewing Entities

- 17.1 Conflict of Interest Committee (COIC)
 - 17.2 Radiation Safety Committee (RAC)
 - 17.3 Clinical Engineering
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17.1 CONFLICT OF INTEREST COMMITTEE (COIC)

The Conflict of Interest Committee (COIC) oversees the Conflict of Interest program by providing advice, assistance and review services on specific written conflict of interest policies and procedures and related activities. This assistance is determined and forwarded through the IRB. The Investigator does not need to forward information to the committee directly.

- } See the Children's policy 1.58 Conflict of Interest Related to Research for more details in the policy section of this manual.
<http://careforce/cms/default.aspx?id=2057>

17.2 RADIATION SAFETY COMMITTEE (RAC)

Overview

All trials that involve machine-produced radiation or radioactive materials or radiopharmaceuticals, including both standard of care and research-related procedures, must be approved by both the Radiation Safety Committee and by the IRB. The IRB approval of the protocol will be designated as approval pending until the radiation safety approval is obtained.

PI Authorization to Work with Radioactive Material

PI who will use radioactive material must obtain authorization to do so from the Radiation Safety Committee or have an authorized user and physician collaborate on the trial. Contact the Radiation Safety office to obtain authorization to work with radioactive material or to request a list of authorized user physicians. Authorizations are renewed every five years.

Radiation Safety Committee Review/Approval Process of Protocol

The PI must submit the following to the Radiation Safety office for all protocols which involve the use of radiation:

1. A copy of the IRB Initial Submission Form, a lay summary of the research, the schedule of events and the informed consent/assent form(s).

There are four types of Radiation Safety Committee reviews/approvals depending upon the type of radiation involved and whether or not the procedure involving radiation is standard of care or research related:

1. Machine Produced Radiation
 - Full committee review by Radiation Safety Committee-III (RSC-III).
 - The review period is two weeks.
 - No renewal required (approval does not expire).
2. FDA-approved Radioactive Materials Used in Standard of Care Procedures
 - Single physician review by a member of the Radiation Safety Committee-I (RSC-I) or referral to full Committee Review by RSC-I.
 - The review period is two weeks.
 - No renewal required (approval does not expire).
3. FDA-approved Radioactive Materials Used in Research-related Procedures
 - Full Committee Review by Radiation Safety Committee-I (RSC-I).
 - The review period is two weeks.
 - Approval requires a renewal every five years.
4. New Radiopharmaceuticals
 - Full Committee Review by Radioactive Drug Research Committee (RDRC).
 - The review period is two weeks.
 - Approval requires a renewal every five years.

Once the protocol has been approved, the Radiation Safety office prepares a hardcopy document and distributes to the PI, clinical research coordinator (CRC) and IRB.

Recommended Informed Consent Form Wording

Recommended wording of the consent form is based upon the level of radiation to which subjects will be exposed:

- Less than annual background
- More than background but less than what a radiation worker could receive annually
- More than a radiation worker could receive

The following core paragraphs are recommended:

"This research study involves exposure to radiation from a (name procedure). This (these) procedure(s) is (are) routinely used for medical purposes. This radiation dose (is/is not) necessary for your medical care and (will/will not) occur only as a result of your participation in this study."

"Women who are or may be pregnant should not participate in this study because of possible effects of radiation exposure on their unborn child. There are currently no studies that show an increase in the risk of genetic mutation in the next generation of offspring."

Case 1, for whole body Effective Dose Equivalent (EDE) <3 mSv (Chest X-ray, Dual Energy X-ray Absorption (DEXA), Extremity Film, Mammogram, Lung Scan):

"The radiation dose that you will receive is equal to or less than the natural environmental radiation the average person receives in the United States annually. The

principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk from radiation exposure of this magnitude is considered to be negligible when compared to everyday risks."

Case 2, for whole body Effective Dose Equivalent (EDE) 3 mSv–50 mSv (Torso Computed Tomography (CT), Angiogram, Positron Emission Tomography (PET) scan, and Bone Scan):

"The radiation dose that you will receive is equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, X-ray technologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation induced cancer from this study is minimal. The risk from radiation exposure of this magnitude is considered to be comparable to other everyday risks."

Case 3, for whole body Effective Dose Equivalent >50 mSv (Multiple Procedures, Therapy, TIPS): "This radiation dose is considered an acceptable risk to subjects. The radiation dose that you will receive is equivalent to _____ times the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for example, X-ray technologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. Excess cancer risk from this exposure may be as high as _____ percent for a person with a life expectancy of 70 years; the risk would be less for persons with a shorter life expectancy."

Case 4, for procedures involving Fluoroscopy:

"The radiation dose that you will receive is equal to or less than the annual radiation exposure limit allowed for persons who are occupationally exposed to radiation (for examples, X-ray technologist and radiologist). The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal. The risk from radiation exposure of this magnitude is considered to be comparable to other everyday risks."

"You will receive radiation exposure from the fluoroscope that produces pictures of your internal organs. Your soft tissue and bones will receive a radiation exposure, but the highest radiation exposure will be to your skin. Very high skin exposures can cause reddening of the skin, blistering and even ulceration. Sometimes this will be delayed for weeks or months after exposure. If you should experience skin discomfort in the area that was pictured, report this to the study doctor or your personal physician."

Human Use Dose Considerations

ADOPTED BY COMMITTEE I—(Radionuclide Use)

Rev. Nov. 4, 1998

Research studies involving the administration of radiation to human subjects and which do not fall under the jurisdiction of the RDRC shall meet the following requirements:

1. The study shall be designed so that the subject receives the smallest radiation dose with which it is practical to perform the study.
2. The study shall be designed to use the smallest number of subjects necessary to achieve the desired result.
3. The study shall be terminated when the desired result is achieved, or when the

hypothesis is determined to have failed.

4. The study shall limit the radiation dose to normal control subjects to less than or equal to:

- 3.75 rem to any organ per 24 hours
- 10 rem to any organ per year
- 3 rem to the whole body per 24 hours
- 5 rem to the whole body per year

5. The study shall limit the radiation dose to persons affected by the disease under study to less than or equal to*:

- 5 rem to any organ per 24 hours
 - 15 rem to any organ per year
 - 3 rem to the whole body per 24 hours
 - 5 rem to the whole body per year
- Note: 1 rad = 10 mGy; 1 rem = 10 mSv.

*Exclusions:

All Therapeutic applications

Protocols which use routine nuclear medicine studies for research purposes rather than clinical purposes and which exceed the above limits will be evaluated on a case-by-case basis.

6. Minors shall not be considered as candidates for human subjects unless the disease under study principally afflicts minors.

7. The Committee recognizes that the International Commission on Radiological Protection (ICRP) recommends radiation dose to minors be limited to 50 percent of the adult radiation dose limits, and that the FDA recommends radiation dose to minors be limited to 10 percent of the adult radiation dose limits. Dose limits to minors will be considered by the Committee if the need arises.

8. Pregnant women shall not participate as human subjects. Women of child-bearing age or potential shall not participate as human subjects unless a pregnancy test has been performed within 24 hours of the study, and the result of the pregnancy test is negative.

9. A consent form shall be used which describes the relative risk of the radiation exposure received due to participation in the study from radioisotopes (11/98). The "Recommended Consent Form Wording"* is representative of the items which shall be included in the consent form.

*Exclusion: The "Recommended Consent Form Wording" provisions are not applicable to therapeutic protocols. (5/96)

10. The researcher shall report to the Committee, by Radiation Safety, semiannually (5/96), the status of his study. The report shall include for the study: The study title, the study status (11/98), the investigator, the radionuclide, the compound, the representative dosage (11/98), the maximum radiation dose to the whole body and to the significantly exposed organs received by a representative subject, the number of subjects studied in the reporting period and any adverse events. (11/98) A form for providing this information is available from the Radiation Safety office.

RESPONSIBILITIES OF INDIVIDUALS

Responsibilities of Principal Investigators or Principal Users:

1. Instruct supervised radiation users in the principles of radiation safety appropriate to that individual's use of radioactive material.
2. Review the supervised individuals use of radioactive material, provide reinstruction as needed, and review records kept to reflect this use. This review must be documented.
3. Be available to communicate with supervised individuals.
4. Permit only those individuals whose names are listed on their authorizations to use radioactive material in their laboratory.
5. Maintain accurate inventories to assure that authorized possession limits are not exceeded.
6. Require that only those individuals permitted under state and local regulations and specifically trained, and designated in writing by the principal user, shall be permitted to administer radionuclides or radiation to patients.

Responsibilities of Registered Radiation Users:

1. Follow the instructions of the supervising principal user.
2. Follow the written radiation safety procedures established in the principal user's authorization.
3. Follow the procedures established by the Radiation Safety office.
4. Comply with state regulations and license conditions with respect to the use of radioactive material.

17.3 CLINICAL ENGINEERING

The Clinical Engineering department at Children's is a member of the Support Services team and participates in the design, teaching, execution, monitoring and improvement of the Medical Equipment Management program. The program provides equipment service and support to aid in the delivery of increased value care. Clinical Engineering serves as a link between clinicians, medical equipment and current health technology.

Functions of the Clinical Engineering department include:

- Maintain safety and function of medical equipment throughout the medical center and community outreach locations.
- Perform equipment prepurchase evaluations.
- Educate and consult medical staff on appropriate applications of technology.
- Manage outside service contracts to maximize effectiveness.
- Establish, support, and maintain the medical equipment tracking system.

- Monitor and promote quality improvement.

The Clinical Engineering definition of a medical device is defined as any electrical device used directly in patient care for the purpose of life support, surgical and/or intensive care, physical therapy and treatment, physiological monitoring or anatomical/physiological diagnostics. These are the types of devices that Clinical Engineering will be involved with.

Medical equipment and/or devices being studied in a research project should be communicated to the Clinical Engineering department at Children's to determine if it meets the criteria for management under the aforementioned program. More details regarding policies and procedures of the Clinical Engineering department can be found at:

http://careforce/cms/menus/documents/policies/Environment_of_Care/6-10.pdf.

18.0 Study Finances and Contracts: Pre-award Process

- 18.1 Study Budget Development
 - 18.2 Final Approval of Budgets
 - 18.3 Contracts
 - 18.4 The Children's Final Approval Process
 - 18.5 Notice of Award
-

For guidance, refer to the Children's Careforce Connection or the Children's public Web site at www.choa.org under the heading For Professionals/Clinical Research.

Study Finances and Contracts: Pre-award Process

Contract and study finances are managed in two, distinct phases: pre-award and post-award. Both pre-award and post-award processes are to ensure compliance with policies and regulations of Children's, the sponsor or funding agency and local, state and federal regulations.

18.1 STUDY BUDGET DEVELOPMENT

Direct Costs

The PI and Coordinator are responsible for negotiating with the Sponsor or funding agency to finalize the study budget. Direct costs all costs of conducting the study and are available to the research staff to pay for the actual costs. Items to consider are:

- Investigator time plus fringe
- Coordinator time plus fringe
- Cost of patient care procedures

- Administrative time for regulatory preparation
- IRB submission fees
- Equipment
- Travel
- Supplies
- Other

Patient Care Budgeting:

The Children's Technical Fees:

- Request costs for the Children's technical fees from the Office of Grants Accounting and Contracts.
- Provide the following information:
 - Name of Project
 - Principal Investigator Name
 - Coordinator Name
 - Funding Source
 - Each procedures required, CPT code if known, detailed description of procedures (i.e., brain magnetic resonance imaging (MRI) scan without contrast, brain MRI with contrast, brain MRI with and without contrast)
- The Office of Grants Accounting and Contracts will provide a written budget.
- Prices are quoted based on current hospital charges and are good for the entire project.
- Research discounting is applied according to funding source.
- Budgets are not interchangeable between funding sources or projects. Charges are subject to change at least once a year therefore, the cost of a procedure priced in June will be different if priced in January.
- The written budget will stay on file in the Office of Grants Accounting and Contracts until the project is submitted for the Children's final approval.

Professional Fees

- If the project involves procedures such as MRI, chest X-ray, electrocardiogram (ECG), etc., a physician interprets the results of those procedures and bills a professional fee.
- The Children's Office of Grants Accounting and Contracts cannot provide budget information for professional fees from physicians at either Emory University or a private practice.
- Coordinators must negotiate research costs with the appropriate entity.
 - Emory physicians: costs can be obtained through SiteMinder®.
 - Private practice physicians: costs are negotiated directly with that practice.
- Arrangements must be made separately for invoicing and paying the professional fee.

Indirect Costs

Indirect costs are allocated to the institution where the study is being conducted and are used to support the research infrastructure within the institution. Indirect costs are an established rate applied to the total direct costs. Direct costs plus indirect costs equals the total project budget.

- **The Children's Rates:**

Federal Government: Current rates can be found at the Office of Grants Accounting and Contracts section of the Clinical Research site on Careforce Connection.

Private Industry: Current rates can be found at the Office of Grants Accounting and Contracts section of the Clinical Research site on Careforce Connection.

External Foundations: Private foundations generally have a set indirect cost amount and it is not negotiable.

Internal (Children's) Foundation: none

- **Emory University Rates:**
Work with the individual Emory Department Research Administrator or check Emory University Web site.
- **Private Practice Rates:**
Each private practice may dictate their own indirect rate based on current overhead costs

To assist in planning the entire project use the Feasibility Assessment and Ancillary Department Approval Form located on the Clinical Research Web site on Careforce Connection under the Office of Grants Accounting and Contracts tab, Forms section: <http://careforce/cms/default.aspx?id=2428>

This form is used for:

- Assessing the project to determine feasibility and provide an overview of the project.
- Determine what patient care procedures are required.
- Budgeting for professional and technical fees associated with the patient care procedures.
- Review and approval of department providing services to ensure that the department can provide the service.
- This form must be completed and signed by appropriate department and submitted to the Office of Grants Accounting and Contracts at Children's as part of the final approval process.

18.2 FINAL APPROVAL OF BUDGETS

If Children's is administering the grant funds, the following approval process is required:

- Private Industry: When the PI and/or Coordinator have reached an agreement with the Sponsor or funding agency, submit the budget to the Office of Grants Accounting and Contracts. The Office of Grants Accounting and Contracts reviews and obtains final approval from the Director of Clinical Research. The budget becomes part of the Research Agreement between Children's and the Sponsor.
- Federal Government: Prior to submitting the research application to the federal agency to which you are applying for funding, the Office of Grants Accounting and Contracts will review the budget, obtain approval from the Director of Clinical Research who will obtain the signature of the Children's Institution Official.
- External Foundations: Submit final proposal to Office of Grants Accounting and Contracts for review and approval of Director of Clinical Research. The Clinical Research department will obtain necessary written approval from the Children's Institution Official.

If Emory University is administering the grant funds, the following approval process is required:

- Create a separate internal budget for Children's to include direct costs and indirect costs.
- Complete the Children's Budget Approval Routing Sheet.
- Submit the original of both documents to the Office of Grants Accounting and Contracts for review. The Director of Clinical Research will sign the Budget Approval Routing Sheet and both documents will be routed with the proposal through the Emory University routing process.

18.3 CONTRACTS

Research studies funded by private industry must have a contract. The contract defines the legal relationship between the parties and specifies each parties' rights and responsibilities during performance of the study. The contract deals with important issues such as indemnification, liability insurance, confidentiality and data ownership. The Office of Grants Accounting and Contracts staff will communicate with the Sponsor to negotiate the terms and language of the agreement prior to final signature.

Research studies funded by federal agencies do not have a separate contract unless Children's is a contracted site to the awarded site (i.e. subcontracts). The grant application face page serves as the agreement. The PI and Institution Official signatures indicate that policies and procedures of the federal government will be followed.

External foundation contracts may vary. The Office of Grants Accounting and Contracts will review each agreement to determine that all necessary elements are included.

Contracts vs. Subcontracts:

- Investigators and research staff are employed by Children's—the contract is between Children's and the Sponsor.
- Investigators and all research staff are employed by Emory University—the contract is between Emory and the Sponsor. Children's will invoice Emory for patient care costs incurred.
- Investigators are employed by Emory University and the research staff is employed by Children's—the primary contract is between Emory and the Sponsor and Emory issues a subcontract with Children's with the sponsor contract as an appendix.
- Investigator is a private practice physician; the research staff is employed by Children's and Children's is administering the study funds—the primary contract is between Children's and the sponsor and Children's will issue a subcontract with the private practice.
- Investigators and research staff are all employed by the private practice—the contract is between the private practice and the Sponsor. Children's will invoice the private practice for patient care costs incurred.

Contract process for Children's:

The Office of Grants Accounting and Contracts at Children's is responsible for the following:

- Legal and Risk Management review
- Resolves issues with Sponsor
- Obtains signature of PI if applicable
- Obtains signature of the Children's Institution Official and Sponsor
- When contract is fully executed, provide the original copy to the Children's Legal department and copies to the PI or Coordinator, Corporate Finance and other appropriate personnel at Children's.

Subcontract process between Emory and Children's:

All research proposals are submitted to the Dean's Office in the College of Medicine at Emory by the home department of the PI. The Business and Finance department review the proposal for accuracy including the Children's Internal Budget and the Children's Budget Approval Routing Sheet. If the study site is Children's and there is not a Children's Internal Budget and signed Budget Approval Routing Sheet the Dean's Office will not process the application. If the study site is listed as Children's but a subcontract is not necessary the Dean's Office still requires signoff by Children's on the Sponsored Program Approval Form (SPAF). If the appropriate documentation is included they approve and forward to the Emory University office of sponsored programs. After the Office of Sponsored Programs and the sponsor finalize the contract, Emory will submit a subcontract to the Office of Grants Accounting and Contracts. Once received the Office of Grants Accounting and Contracts is responsible for the following:

- Legal and Risk Management review
- Resolves issues with Sponsor
- Obtains signature of PI if applicable
- Obtains signature of the Children's Institution Official and Sponsor
- When contract is fully executed, provide one original copy to the Children's Legal department and return one original copy to Emory University with copies to the Children's Research Coordinator, the Children's Corporate Finance and other appropriate personnel at Children's.

Subcontract process between and Children's and private practice:

The Children's Office of Grants Accounting and Contracts is responsible for the following:

- Creating subcontract between Children's and the Private Practice.
- Legal and Risk Management review of sponsor agreement and subcontract.
- Resolves issues with sponsor and private practice.
- Obtains signature of Principal Investigator if applicable and Private Practice Administrator.
- Obtains signature of the Children's Institution Official and Sponsor.
- When contract is fully executed, provide one original copy to the Children's Legal department with copies to the private practice, the Children's research coordinator, the Children's Corporate Finance and other appropriate personnel at Children's.

18.4 THE CHILDREN'S FINAL APPROVAL PROCESS

- All projects must have administrative approval of the Director of Clinical Research at Children's.
- This is not an IRB issue, the IRB process is independent from the grants accounting and contracts process.
- This approval ensures that pre-award processes are complete.

Process for the Children's Projects

Submit the following to the Office of Grants Accounting and Contracts:

- Feasibility Assessment and Ancillary Department Approval Form (signed by each department at Children's being utilized).
- Copy of the IRB Approval Letter from the Children's IRB.
- Patient Care Budget
- Fully executed contract
- Grant Activity account

Process for Emory Projects

Submit the following to the Children's Office of Grants Accounting and Contracts:

- One complete copy of the Emory IRB Submission with the Approval Letter and a copy of the approved informed consent.
- Children's Research Approval Form.
- Patient Care Budget
- If applicable, the fully executed subcontract with Emory
- The Children's Grant Activity (activated if needed)
- Research Approval Form signed by the Director of Clinical Research

18.5 NOTICE OF AWARD

Upon receipt of a fully executed contract, the Office of Grants Accounting and Contracts will open a Grant Activity account with Corporate Finance.

A Notice of Award will be sent to the PI and/or Study Coordinator and the Children's Corporate Finance. The notice of award will include the following:

- Name of Study
- Sponsor
- Children's Grant Activity Number
- Budget Information
- Terms and Conditions of Payment

} See the Children's Standard Operating Procedure: Negotiating Research Contracts (Appendix H), Amendments To The Research Contract (Appendix I), Letters of Agreement (Appendix J)

} For more information see the following the Children's policies: Research Contracting 1.40, Patient Care Budgeting for Sponsored Research 1.41, Sponsored Research Budgets 1.52, Effort Reporting 1.53 <http://careforce/cms/default.aspx?id=2057>

19.0 *Site Implementation*

- Multicenter trials are studies that are managed at more than one center. Site implementation is the process of organizing everything that is needed for a center to participate in a clinical trial.

19.1 Site Selection for Multicenter Studies

19.2 Site Orientation

19.3 Site Initiation

19.1 **SITE SELECTION FOR MULTICENTER STUDIES**

Sponsor Site Assessment

- Once the protocol is developed and ready for implementation, the Sponsor must select investigative sites. Sponsors seek sites with qualified and experienced Investigators and well-trained support staff. Because research nurses and coordinators play such a critical role in the success of a clinical trial, trained site staff can heavily influence selection.
- After sites have been identified, sponsors assess the level of interest by asking investigators to review the protocol. The Sponsor must also assess site feasibility by conducting a site visit to evaluate the facilities and the research team's abilities.
- In addition to qualifications, sites are selected based on their enrollment projections. The number of sites selected is determined by the number of patients required, a need for broad geographic distribution, the length of the trial and the sponsor's monitoring resources.
- The sponsor of a clinical trial will identify prospective investigators, and then determine if the investigators and the investigative sites qualify to participate in the trial according to the Sponsor's criteria. The Sponsor may consider the following items for a prospective clinical trial site:
 - Investigator's clinical expertise and reputation
 - Study staff competence
 - Access to patients
 - Facilities and equipment
 - Investigator's level of cooperation
 - Investigator's level of accessibility
 - Time and cost factors
 - Site location

After a PI has returned a signed Confidentiality/Nondisclosure Agreement, the PI will usually receive the following materials:

- Preliminary study-specific questionnaire (if not previously sent)

- Study synopsis and/or draft protocol and amendments
- Patient information leaflet, informed consent form and consent procedures
- Investigators Brochure (IB), if available
- Financial and contractual agreements to be used
- Regulatory standards and requirements related to the trial

The Sponsor will seek from the PI additional information, which may include:

- Request for current curriculum vitae (CV)
- Name and address of the IRB to approve trial
- Other approvals needed, e.g., institutional departments
- Safety issues and PI reporting responsibilities for Adverse Events (AE)
- Other research commitments, e.g., other trials using the same patient pool
- Number of patients eligible for participation in the trial, with supporting evidence, if possible
- PI clinical trial experience
- Contact details for the clinical laboratory or other participating department(s)
- General clinic operations, including hours of operation and weekend staffing procedures

Based on the site's criteria of a desirable study and the information received from the prospective site, the Sponsor/Clinical Research Associate (CRA) will make follow-up phone calls to the prospective investigator(s) to discuss the protocol in more detail and to learn more about the site's capabilities including the population of patients meeting the enrollment criteria.

Site Qualification Visit

If early communications lead both parties to believe that the study site will participate in the trial, the Sponsor's representative will visit the site for a final assessment. Issues to be considered may include:

- Investigative site's written Standard Operating Procedures (SOPs)
- Support staff, e.g. Research Nurse, Site Coordinator
- Test article accountability requirements and responsibilities
- Adequacy of protocol required equipment, including maintenance and calibration records
- Acceptable security, space and storage conditions for test articles, study materials, and study binders and documents
- Clinic follow-up space and time
- Clinical Laboratory certification and normal ranges
- Current CV of Investigator, Laboratory Director
- Involvement of other departments, e.g. Pharmacy, Radiology, etc.
- Agreement to allow quality assurance audits as required
- Adequacy of computerized systems

19.2 SITE ORIENTATION

Investigators Meeting

- Industry-sponsored clinical trials with multiple sites typically invite all investigators and clinical research coordinators (CRC) to a meeting at which the details of the trial are presented, questions answered, and the sponsor's staff has the opportunity to meet the investigators and CRCs. It is imperative that the research

investigators and staff thoroughly read and understand the protocol procedures, requirements and the risks to volunteers. The investigators' meeting is the customary method for the sponsor to assure this understanding is adequate.

Regulatory Documents Binder and Financial Document Binder

For each trial, all clinical trial documentation is to be kept in two separate binders: nonfinancial documents in the Regulatory Documents binder and financial documents in the Financial Documents binder. In the case of an FDA audit, the Financial Documents binder is not provided to the auditor. Depending upon the length and size of the trial, the Critical Documents binder may consist of several volumes.

19.3 SITE INITIATION

To ensure that the Investigator and the support staff are well prepared to carry out their obligations in conducting a clinical trial, the Sponsor sends a monitor to assess the site's preparedness.

NOTE: In studies in which the Investigator is also serving as the Sponsor, the Investigator is responsible for performing all monitoring duties.

Document Review

The following is a typical checklist of documents and information that will be reviewed by the Sponsor/Monitor at the Site Initiation Visit:

- Signed Confidentiality/Nondisclosure Agreement
- Signed contract with approved budget
- Signed protocol (including all amendments)
- Investigator's Brochure (IB)
- Signed Statement of Investigator (Form 1572)
- CVs and copies of medical licenses of all staff listed on Statement of Investigator
- Name and address of approving IRB
- IRB membership List or IRB federal-wide assurance number
- IRB letter of approval of the protocol
- Copy of IRB-approved and date-stamped informed consent form and procedures for obtaining informed consent
- IRB approved copy of any advertisements
- IRB approved compensation to trial subjects
- Authorized Personnel Signature form
- Signed responsibility assignment log
- Clinical Laboratory certification and normal ranges
- Randomization schedule
- Log for patient screening and enrollment
- Correspondence file
- Monitor sign-in log

Protocol and Regulatory Review

The following items should be reviewed with study staff as part of the Site Initiation Visit:

- Study objectives
- Inclusion/exclusion criteria
- Study procedures

- Procedures for dropout, discontinued and replacement subjects
- Special laboratory procedures
- Study-monitoring schedule
- Reporting requirements for adverse events (AE) and Serious Adverse Events (SAE)
- IRB reporting requirements
- Reporting of protocol deviations
- Consenting requirements
- Long-term retention of trial-related documents
- Method for the completion and correction of Case Report Forms (CRFs)
- CRF signature requirements
- Importance of timely completion of CRF entries
- Source documentation: creation, location, reference and access
- Review of study supplies and reconciliation with shipping order
- Storage of investigational agents (drug, biologic or diagnostic) or devices
- Review of written procedure for proper handling and dispensing of study supplies
- Tracking system and log for dispensing and return of investigational agents
- Handling of trial-related supplies
- Investigational agent accountability records

Section III Research Project Management

20.0 General Guidelines of Study Management

- 20.1 Tracking Key Parameters
- 20.2 Study Management Meetings

20.1 TRACKING KEY PARAMETERS

Successful study management should involve the tracking of key parameters in all aspects of the study throughout the entire duration of the study. Tracking of key study parameters can serve as tools to ensure that study startup occurs within the anticipated time frame, enrollment expectations and milestones are met, regulatory adherence is followed and good clinical practices (GCP) compliance is met.

Some key parameters to consider when tracking are:

Study Startup:

- Contract and budget readiness
- Regulatory readiness
- Site logistics readiness (internal feasibility assessment)
- Staff education
- Sponsor readiness

Study Conduct:

- Subject enrollment rate
- Subject safety and efficacy
- Data collection and submission
- Adverse Event (AE)/Serious Adverse Event (SAE) data collection and submission
- Drug and/or device accountability
- Adoption and use of protocol amendments
- Regulatory adherence
- Communication with the Sponsor, clinical research organization (CRO), IRB and other applicable research agencies

Study Closeout:

- Data clarifications
- Return/disposal of drug/device as instructed
- Notification to the proper agencies of study closeout
- Record Storage Procedures

20.2 STUDY MANAGEMENT MEETINGS

Study management meetings can be very beneficial to the success of a study. They often occur monthly and anyone involved in the study is encouraged to attend. This is time set aside to focus on the study and a time to discuss concerns, issues and the progress of the study. This also helps educate everyone on all aspects of the study including the protocol.

21.0 *Study Documentation Management*

- 21.1 Regulatory Binder—General
- 21.2 Regulatory Binder—Additional Elements for Drug and Device Studies
- 21.3 Manual of Operations
- 21.4 Financial Documents

21.1 REGULATORY BINDER—GENERAL

The regulatory binder is used to keep all the important documents necessary for any study—sponsored or unsponsored. Often with sponsored studies the regulatory binder is provided. An organized binder is essential during a monitoring visit.

Some the basic tabs you will find in a regulatory binder are:

Protocol: The most recent version needs to be first (save previous versions)

Protocol Amendments: Any amendments to the protocol for quick reference

Protocol Signature Page: The signature page is signed by the PI ensuring they are familiar with the protocol and any amendments

1572: FDA form 1572, with the current one first (or investigator agreement for device studies)

Correspondence: Any correspondence or general notes

CV: The curriculum vitae of the study personnel

IRB Approvals: Approval letter, modifications, renewals or any other IRB approval documents

IRB Approved Informed Consent: The IRB approved consent forms with most recent version in front

Data Safety Monitoring Board Reports/Serious Adverse Event Forms: Any safety reports or FDA reports regarding the study or drug

Logs: Logs relating to the study conduct, including the signature log, shipment logs and site visit logs, subject enrollment log and drug accountability log

Lab Normal: Lab normal ranges for your site

Lab Certifications: CLIA and Lab Director CAP certification

Package Inserts: If this is a pharmaceutical study, the package inserts are printed and kept for reference

Investigator Brochure: Official document supplied by the sponsor outlining clinical findings, side effects, directions to the investigator, etc.

See the Children's policy regulatory binders for Clinical Research in the policy section of this manual.

21.2 REGULATORY BINDER—ADDITIONAL ELEMENTS FOR DRUG AND DEVICE STUDIES

Drug and device studies often have additional sections located in the regulatory binder. Some of these are:

Package Inserts: Inserts that detail information about the side effects and pharmacology of the medicine.

Device Manufacturer Information: Information about where the device is made, including contact information for questions about the device.

Device Application: Application submitted to the FDA for approval containing information about the risk the device poses and testing history. Prior to initiating a clinical trial for significant risk (SR) device studies, sponsors must file an

investigational device exemption (IDE) with the FDA before they may start the clinical trial. This is not required for nonsignificant risk (NSR) devices used in a clinical trial. To start the only requirement is IRB approval.

Serious Adverse Event (SAE)/ Emergency Situations: SAE process and any emergency contact number and information

21.3 MANUAL OF OPERATIONS

A Manual of Operations is designed to highlight research processes specific to a clinical trial. This manual is typically sponsor provided and intended to serve as a guide for study personnel in conducting a clinical trial. Contents of the manual may include:

- The study protocol and process
- Substudy protocol and process
- Subject enrollment instructions
- Investigator and patient or parent education materials
- Core laboratory procedures
- Data collection forms and quality control
- Code lists for classifying procedures or diagnosis

21.4 FINANCIAL DOCUMENTS

Financial disclosure is a requirement for clinical investigators for applicable clinical trials (also referred to as covered studies) to disclose potential conflict of interest due to certain financial arrangements and for sponsors to actively seek and report such information to the FDA. The regulations do not prohibit such financial arrangements, rather, the law stipulates that conflict must be disclosed and reported. Furthermore, if such a conflict exists, steps must be taken to minimize the potential for bias. The disclosure includes the investigator's immediate family and the research staff, or research staff's immediate family.

Financial disclosure regulation went into effect Feb. 2, 1999, Sponsor companies (also referred to as applicants) must submit financial disclosure information to the FDA along with their marketing application. Financial disclosure is not retroactive to submissions prior to Feb. 2, 1999.

Financial conflict of interest may pose a threat to a trial as it could be source for investigator bias. The FDA may consider a clinical study to be inadequate if appropriate steps are not taken to minimize bias in design, reporting and analysis.

A financial disclosure must be reported from the time when an investigator first begins the study to a period of one year thereafter following the completion of the study. Most sponsors will collect the information at the beginning of a study. Investigators are obligated to promptly update the information if any relevant changes occur during the course of the investigation. Sponsor Standard Operating Procedure dictates the format and timing of financial disclosure information collection.

The financial information that must be disclosed is:

- Compensation related to the outcome of the study
- Proprietary Interest in the product
- Employment of consulting relationship of more than \$10,000
- Equity ownership in the sponsor company greater than \$50,000
- Other payments (excluding the cost of the study) to the investigator greater than \$25,000

An Investigator obligation is to disclose information as requested, update information when appropriate and recordkeeping.

The sponsor obligations are to educate clinical investigators regarding financial disclosure requirements, diligently seek financial disclosure information from clinical investigators, provide a list of all clinical investigators who conducted covered studies under the FDA, and submit for each investigator that no financial arrangements exist or disclose the nature of arrangements to FDA.

The FDA will evaluate financial disclosure information and determine if there is an impact on the reliability of the study data. The size and nature, as well as steps taken to minimize bias, will be taken into consideration at the time of evaluation. The design and purpose of the study is also an important consideration when determining the impact of financial conflict of interest.

The FDA can refuse to file the marketing application if they feel there is a conflict of interest. They may also request additional analysis, request additional confirmatory studies and even refuse data.

22.0 Data Management

- 22.1 Data Dictionary
- 22.2 Creating the Study Database
- 22.3 Testing
- 22.4 Statistical Analysis
- 22.5 Location of Database
- 22.6 Transfer of Information

Data Management

The purpose of this section is to provide some guidance for working with primary (conversion of completed data collection forms into accurate, complete data sets) and/or secondary (existing data collected primarily for other purposes) data sets to be analyzed statistically.

Data management ideally begins before the study begins. Before you enter, manipulate or analyze data, it is important to prepare for this process. Doing this helps ensure the quality of your data and a better understanding of all the measures.

Study team members should determine hardware and software that will be used to manage the data, format of the database, and determine how data will be entered and edited. Only after thorough testing of data management procedures, data entry and editing for the study begins. A record is kept of any changes in the database, and regular backups are made with storage in secure locations. At the end of the study, analyses are conducted, and the original data (either on paper or, preferably, electronically) are archived and stored.

22.1 DATA DICTIONARY

Creating a data dictionary includes defining or coding each variable, assigning a name and defining the variable format and the range of permitted responses. The data dictionary makes data entry and analysis much easier. It is best practice to develop a data dictionary for any research project with which you work. The data dictionary should have the following elements:

1. Question as written on case report form or other source document
2. Name of the variable as named in the database
3. Level of measurement (nominal, ordinal, scale)
4. Response type (numeric, string, etc.) and categories
5. Response values and labels
6. Applicable logic checks

1. Question as Written on Case Report Form or Other Source Document

For example, if you have the following question on the Case Report Form, "Did you smoke during pregnancy" (Question 1), you restate the question in this section so you can verify that you are referring to the same information.

2. Name of the Variable as Named in the Database

Using the data collection forms, each variable should be identified and given a name. This variable name will subsequently be used to identify variables in the database and for analysis. Each variable should have an abbreviated name that helps describe the data instead of generic names—e.g. "Question 1." This convention makes it easier to read analysis output. Variable names should be short but understandable and consistent. For example, a variable that collects data on the age at which a participant was diagnosed with cystic fibrosis might look like "agedxcf." Abbreviations should also be used consistently.

For each variable, the data dictionary should include the **type**, **format** and the **permissible values** that can be entered in the database.

- **Variable types** include **continuous**, **integer** and **free text**.
 - **Continuous:** typically number variables in scale order, for example, temperature
 - **Integer:** number with no specific scale order, for example, street number

- **Free text** data must be coded for analysis, a procedure that is time-consuming and prone to errors. For example, medications used during a study are often collected as text data. If the researcher knows in advance that he will be interested in whether the patient is taking a diuretic, it is best to have a yes/no item for diuretic use on the data collection form. If the data on medications are free text, the researcher will need to parse the text for strings of characters, such as "furos" or "Lasix," to identify subjects who took furosemide. A frequency tabulation of all text strings indicating medications should then be scanned to make sure no other strings likely indicating furosemide have been missed. Sometimes it is helpful to include free text that will not be analyzed to provide salient information about the participant or the visit that can then be visually scanned by the staff investigating records. For example, a "notes" field might include the text "subject grossly obese; weight is 440 pounds" to clarify the extreme value for a subject whose weight is entered as 200 kilograms.
- **Variable Format:** If a number, need to know currency, decimal places, date, etc. (for example, mm/dd/yyyy vs. mm/dd/yy). For alpha-numeric variables, you need to decide how many characters spaces and caps/no caps to allow. (for example, M or F for male or female would be one character vs. a comment or note which would be up to or more than 255 characters.
- **Permissible Values:** Once each variable has been named and the type and format defined, a range of permitted values can be assigned. For dichotomous variables only two discrete values (plus missing) are allowable. For continuous variables, deciding on the allowable range may be more difficult. The purpose of defining variable ranges is to guide data editing. Values outside the defined range must be checked for accuracy. If the range set for continuous variables is too wide, inaccurate values may not be identified. In contrast, if the range is set too narrow, many accurate values will need to be checked and verified.

Consistent rules should be used to code variables. For example, a variable on a data form is answered as yes or no, the data code might be 0 or 1, where a 0 represents no and 1 represents yes. It is good practice to be consistent when coding dichotomous variables. In particular, a 0 should always represent no or absent, and 1 should always represent yes or present. With this coding, the average value of the variable is interpretable as the proportion with the attribute. Missing data should be assigned a value that is not a possible numeric value because analysis programs treat the code as data. For example, if missing data are coded "99", a subject who has a missing value for age will actually be analyzed as if age is 99 years. Missing data are often coded "." It is best to code "don't know" differently from missing data because the implications for editing and analyzing the data are different. In addition, some variables are supposed to be missing because the data are not applicable. Some software programs allow several codes for missing, such as ".a" for missing, ".b" for don't know, and ".c" for values that are not applicable. In the analysis, all these values are treated as missing, but the reason the data are missing is retained.

3. Level of Measurement (Nominal, Ordinal, Scale)

It is helpful to categorize the data by its level of measurement. During analysis these levels are analyzed differently. Nominal data refers to most to values with no inherent order. For example, gender is nominal data with two values, male and female. Ordinal data refers to values with an inherent order. For example, low acuity and high acuity. Scale data refers to values that have both inherent order and specific intervals—for example, age.

4. Response Type (Numeric, String) and Categories

Specify, in advance, the response type in the form that it will be saved in the database. These responses are saved as either numbers or characters. It is also important to indicate categorical responses ahead of time. For example race is usually reported as predefined categories following a specific convention.

5. Response Values and Labels

This section specifies the predefined exhaustive list of response values and their associated label descriptions. For example, the number five equals extremely satisfied on a five-point Likert scale. The list would then continue to define the remaining four values.

6. Applicable Logic Checks

Data can be verified using predetermined logic checks. For example, an individual's reported age equals the calculated age using their date of birth. It can also be used to check completeness of reporting. For example, if a question for hospitalization is answered yes, then the section for hospitalization must be completed.

22.2 CREATING THE STUDY DATABASE

Spreadsheets

Perhaps the most common and easily accessible approach to creating a simple database is to use a spreadsheet program and then transfer the data to statistical software for analysis. Spreadsheets arrange data in a matrix of rows (for the study subjects) and columns (for the variables) called a table or flat file. Data editing in a spreadsheet is generally a simple matter of comparing the values in the database with the values written on the data collection forms. Spreadsheets generally do not provide good tools for creating a data entry interface or for performing automatic or interactive data editing. Spreadsheets do not provide record level integrity functions which sometimes unknowingly results in corrupt data.

Spreadsheet programs can produce simple reports and calculate basic statistics. However, it is typically easier and more efficient to transfer the database after entry and editing into a statistical program for data analysis. Data transfer is generally quick and easy, as most statistical analysis programs can read data directly from spreadsheets.

Relational Databases

Most studies use relational databases for data entry, editing and management. Some of these packages also provide powerful interface builders for data entry. Interfaces allow

the data entry screen to be formatted to resemble the data form and facilitating data entry. Data can then be entered uncoded and automatically translated by the program into the correct data format in the database. Interface builder software can also be used with other software to perform this function.

Relational database programs typically allow researchers to easily perform double data entry in which the data are entered twice and discrepant values are identified for correction. Automatic range and logic edits can also be established, and editing can be done interactively, so that the data entry operator is prompted to correct missing, out-of-range or illogical values at the time of data entry. These software packages can also be programmed so that data entry can be done by machine-readable forms or voice recognition.

A relational database includes multiple-related tables. Additional subtables might contain data on severity of the cancer (size, stage, grade and histologic type), information on genetic markers found in the cancers, and surgical outcome for those subjects who underwent surgery. The same information could be stored in one large table, but many of the cells would be inapplicable, since only a minority of the subjects will develop lung cancer. This type of relational database allows efficient data editing and management, because only the tables involved in specific editing procedures are used.

In contrast to spreadsheet programs, relational database software provides powerful tools to ensure that related tables are complete and accurate across complex databases. Relational database software provides powerful and flexible programming tools, the ability to handle multiple, related data tables and to produce flexible and complex reports. Creating and customizing the program may require substantial time and expertise, and the complexity of the editing and checking parameters makes modifications difficult if there are changes in the data collection forms. The statistical analysis capability of relational databases is limited, and data are usually transferred to another software package for data analysis.

Examples of programs used to create databases:

Spreadsheet—Microsoft Excel

Relational Database—Oracle, Microsoft SQL Server and Access

Enterprise Manager—Oracle and Microsoft SQL Server

Statistical Analysis Package—Statistical Analysis System (SAS), Statistical Package for the Social Sciences (SPSS), Stata, Epi Info, Minitab

Machine Readable Forms—Teleform

Interface Builder—Microsoft Access, Power Builder, Visual Basic, Epi Info

22.3 TESTING

Test the data management system before the study begins. The entire database system (forms, coding, data entry, data editing, query management and data transfer) should be tested using dummy data. Test forms can be completed and the data entered, edited, and transferred for analysis using the methods planned for the study. Dummy data forms can include variable values that are missing, out of range and illogical to make sure that

the data editing system is correctly identifying errors. When malfunctions are identified, they should be corrected and the system retested until it works correctly.

22.4 STATISTICAL ANALYSIS

Statistical analysis software packages provide basic data entry and editing modules, but it is generally easier to enter and perform basic data editing using either spreadsheet or relational database software and subsequently transfer the data for analysis. Statistical analysis software also provides very powerful graphic report generation functions. Enterprise management software is used by most research sponsors and professional research organizations. This software allows the user to perform uniform procedures on multiple study databases simultaneously.

Several steps are required to prepare a data set for analysis. Generally, a copy of the database is transferred to statistical analysis software. Variables are often redefined and new variables created. For example, continuous variables may be dichotomized (blood pressure above a cutpoint defined as hypertension), new categories created (specific drugs grouped as antibiotics), and derived variables defined (e.g. asthma severity score). It is desirable to decide how missing data will be handled. "Don't know" is often recoded as a special category, combined with "no," or excluded as missing. Many responses that are "not applicable" (such as the number of live births for women who report never being pregnant) are recoded as the appropriate response ("0" live births) for analysis.

When multiple manuscripts are written based on the same database, it is desirable to use the same definitions of variables and handle missing data in the same way for each analysis. For example, it may be puzzling for readers if the number of diabetic participants in the study varies. This could easily happen if diabetes is defined as self-reported diabetes in one analysis and reported use of hypoglycemic medications in another.

The database should be completely edited and frozen before any final analyses for publication begins. All procedures used to create an analysis-ready dataset should be clearly defined in the data dictionary and in a well-documented data management program.

22.5 LOCATION OF DATABASE

Please refer to the Children's Policy 8.01, Information Management, Electronic File Naming Policy. To facilitate routine business and clinical activities employees may store PHI in databases, spreadsheets and other applications that are not part of Children's core systems. Under no circumstances should clinical processes be designed to be so dependent upon these satellite databases/spreadsheets that core systems and the original paper chart would not provide satisfactory backup in the event that the satellite database/spreadsheet was unavailable. The intent of this policy is to ensure that the

privacy and security of PHI is not compromised by the use of noncore data repositories of PHI.

Storing research databases on network drives with user-level security is the best practice (as opposed to local workstation drives) as it greatly reduces the risk of corruption and/or loss of data during hardware failure and outages. Use of flash drives and other removable/portable media are discouraged due to the significant risk from loss and theft of the device.

22.6 TRANSFER OF INFORMATION

Please refer to the Children's Policy 8.01, Information Management, Electronic File Naming Policy.

Data may not be transferred from a repository to another location on the network without authorization from the owner, the security officer and appropriate password protection. No one is authorized to make electronic copies of a repository containing PHI by tape, diskette, or microfilm or other electronic medium without the knowledge of the owner.

23.0 Investigational Product Inventory

- 23.1 Background and Purpose
- 23.2 Contacting Investigational Pharmacy Services (IPS)
- 23.3 Dispensing
- 23.4 Documentation

23.1 BACKGROUND AND PURPOSE

- The Investigational Pharmacy Services (IPS) of the Department of Pharmacy is responsible for acquisition, control, and maintenance of study medications and records (see Pharmacy Policy #23-00, #23-01 and #23-02—located on Careforce Connection—Pharmacy/Department Policies and Procedures/Patient Care Services/Investigational Drugs).
- Research at Children's that involves the investigational use of drugs, biologics and dietary supplements must be in compliance with the policies and regulations of Children's and Emory University IRBs, the State Board of Pharmacy, the Food and Drug Administration (FDA), and recommendations of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) concerning the use of investigational drugs.
- The IPS works closely with clinical and distributive pharmacy services to support clinical research and to ensure regulatory compliance and patient safety.
- The management of investigational drugs will conform to system-wide medication management practices and to the standard operating procedures at the Children's participating pharmacy locations in order to provide the highest quality service and patient safety.

23.2 CONTACTING INVESTIGATIONAL PHARMACY SERVICES (IPS)

Contact Investigational Pharmacy Services (IPS) as early as possible if your research involves medications of any kind, whether investigational new drugs or FDA-approved drugs for new indications, as part of treatment protocols or for diagnostic or screening purposes. There is often some element of the drugs' acquisition, dispensing, use, billing, etc., that differs from our standard operating procedures. It is best to determine if there are any such differences in advance and plan accordingly to avoid any unwanted and costly delays in opening your protocol.

1. Examples:

- a. *Drugs used for diagnosis or screening.* A pulmonology protocol requires a methacholine challenge as part of the screening process before assigning the subject to different environmental control measures. Even though drug treatment is not part of this protocol, subjects were seen at Children's for the methacholine challenge and the drug supplies were provided by the National Institutes of Health (NIH). In this case, the IPS made special arrangements for these supplies, preparation and billing for the methacholine challenge.
- b. *Testing a new imaging technology that uses a standard imaging agent.* The Joint Commission requires pharmacists to review any imaging agent orders for all patients. If an imaging agent was used concurrently with the imaging technology, the Pharmacy department would be responsible for obtaining, maintaining and dispensing the imaging agent.
- c. *Special ordering for FDA-approved drugs.* An NIH protocol is comparing two standard treatments. Both treatments are FDA approved and considered standard of care. The manufacturer of one of the treatments has donated a supply to the NIH for subjects on this study and needs to be ordered in advance for each new subject. In this case, the IPS can handle the ordering, storage and management of this product including computer order entry and billing.
- d. *Special payment arrangements.* Another NIH protocol comparing different standard treatments has reimbursement provisions from the manufacturer for one of the drugs if it not covered by the subject's insurance.

Before submitting any drug-related protocols to the IRB, consult with IPS. This can help the Investigator avoid unnecessary delays in implementing his/her protocol. All medications administered and/or dispensed at any Children's location are under control of the Pharmacy department and all investigators, regardless of their employer or governing IRB, are required to work through the IPS whenever drugs are involved in their research.

- Be sure to discuss the feasibility and cost of study initiation, management of clinical supplies, drug preparation, compounding and dispensing, documentation and record management, regulatory and sponsor visits, patient and staff education, and other elements of the protocol. These discussions can often discover potential barriers to the practical implementation of a protocol that are much easier to correct in advance, avoiding the lengthy process of rewriting a protocol and resubmitting it to the IRB.
- All IPS charges and fees must be agreed upon prior to initiating the protocol. The IPS will prepare a budget proposal for pharmacy services

required for the protocol. The IPS may charge for services such as study initiation, maintenance, closure, monitor visits, randomization and blinding.

- A copy of the Children's IRB approval letter is required before investigational drugs can be dispensed for a protocol.
- If your study is approved by the Children's IRB, please submit a copy of the approval letter to IPS.
- Studies approved by the Emory IRB require an approved signature from the Children's Director of Clinical Research. Please review the IRB Authorization Agreement, if necessary.

23.3 DISPENSING

The IPS will work closely with the principal investigator's team to develop a dispensing plan that is feasible, practical, meets protocol requirements and medication management standards. Consideration for each of the following items will assist in developing the dispensing plan:

- Location
 - Which hospital campus will be involved?
 - Where will patients be encountered?
 - Where will the drug be administered?
 - In the hospital to inpatients
 - In the clinic to outpatients
 - At home
- Storage requirements
 - The IPS can accommodate room temperature and refrigeration storage at all dispensing locations. Options for storage of frozen (-20 freezer units or -70 or colder freezer units) are limited and may require special procedures.
- Contact information
 - The PI should supply the contact information (telephone, pager and e-mail) for persons who are listed on the protocol IRB application, including all approved prescribers.
- Epic order entry and eMAR requirements
 - In almost all cases, it is required to have the study drug "loaded" into the Epic drug database. The IPS will work with the PI to ensure that all pertinent information about the study drug is added to the drug file to ensure accurate order entry, preparation, labeling (see below), dispensing and administration.
- Labeling
 - All study drugs must be appropriately labeled. Labeling requirements differ depending on where the study drugs are dispensed or administered. The IPS will ensure that the labeling is appropriate and complete.
- Preparation
 - Doses of study medications will be prepared according to the protocol. Sometimes preparation instructions in the protocol differ from preparation practices at Children's. The IPS will work closely with the pharmacy staff to identify potential problems and develop safeguards, procedures, and/or training to ensure proper preparation of doses.
- Dispensing

- The IPS works closely with the appropriate clinical pharmacy services to dispense the study drug when and where it is needed in an efficient and safe manner. This is determined by a number of factors, such as storage and dispensing locations, time of day and special handling requirements.
- Pick-up and/or delivery
 - After the study medications are prepared and ready to dispense, they may be picked up from the pharmacy or delivered to the investigator or other team members. The objective here is to get the study drug to where it is needed in a manner that respects the time and effort of the research subjects and their families.

23.4 DOCUMENTATION

- The basic documentation requirement for almost all protocols is essentially the same. However, there may be a number of additional data elements and/or forms that differ from one protocol to another. Many sponsors provide their own forms or templates, while others will accept generic forms.
- A drug accountability log is required on all studies. The receipt of study drugs from the Sponsor, dispensing and returns are documented on this form. This log must be maintained as a perpetual inventory where the number of units of the study drug available must always match the log. If any discrepancies are found, they should be investigated and resolved as soon as possible.
- Patient specific logs are often used when a Sponsor wants to keep track of more than just the number of units of study drug come and go. Patient-specific logs are helpful when:
 - The study drug is dispensed many times to the same patient
 - Multiple ingredients are used to compound a single dose
 - Calculation of the proper dose is complicated
 - The study drug has limited stability or expiration dating
 - A patient-specific drug supply is sent for each new patient
 - Patient compliance assessments are needed at each visit
- Return and destruction logs. Careful control of each and every unit of study drug is an important part of many protocols and complete documentation may include a record of any drug returned unused by the study patient or not administered by the nurse. A place to document this information can be on a separate form or incorporated into one of the above forms.

	Where does the investigational therapy continue or end?	
Where does the investigational therapy begin?	Inpatient	Outpatient
Inpatient	Label: inpt	Label: both inpt and outpt Rx
Outpatient	Label: both inpt and outpt Rx	Label: outpt Rx

24.0 *Adverse Event Management*

- 24.1 Definitions
 - 24.2 Documentation
 - 24.3 Reporting Serious Adverse Events
-

24.1 DEFINITIONS

An **adverse event** (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

A **serious adverse event** (SAE) is any adverse experience occurring during the course of the study or during planned follow-up. Any adverse event that meets **any of the following criteria** MUST be reported to the Children's IRB:

- Results in death
- Is life-threatening (places the patient at immediate risk of death from the experience as it occurred);
- Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions)
- Results in medical or surgical intervention
- Results in or prolongs an existing inpatient hospitalization (even if the hospitalization is a precautionary measure for observation)
- Is a congenital anomaly/birth defect in offspring of subjects taking the product regardless of time to diagnosis
- Is a cancer
- Is the result of an overdose, whether intentional or accidental, including a breach of protocol
- Is medically unexpected, regardless of severity

An **unexpected adverse event** is any adverse event that is not consistent with the currently approved research protocol, investigator brochure or informed consent form, or one that is not part of the normal disease progression.

An **expected adverse event may qualify as unexpected** and therefore be reportable IF the expected adverse event occurs more frequently than normal.

Adverse events that have occurred **at other sites** must be reported only if they are both serious and unexpected and probably related to the research.

24.2 DOCUMENTATION

Documents to be submitted: The Children's IRB office shall receive the following documents to allow for substantial and meaningful review of the event:

- i. Serious Adverse Event Report Form (At a Children's Location or At a Non-Children's Location): The only exception is if the Children's IRB has deferred review and approval to the Emory IRB per the terms of the signed Authorization Agreements; in that case, the Emory IRB Unexpected Adverse Event Report Form shall be submitted instead of the Children's version of the form.
- ii. A narrative describing the occurrence written in sufficient detail to allow for a thorough IRB evaluation.
- iii. Any additional supporting documentation available to the investigator to aid in the IRB consideration of whether the event suggests adequate human subject protection mechanisms are in place or action is needed.
- iv. Any study documents modified as a result of the occurrence. These will be processed as an amendment to the study and the requirements for submission of requests for modification should be followed.

24.3 REPORTING SERIOUS ADVERSE EVENTS

Prompt reporting is required because some serious adverse events (SAE) require modification of study procedures, research protocols and/or the informed consent forms. It is the responsibility of principal investigators to report in writing **any SAE or unanticipated adverse events** associated with the use of either investigational drugs or devices to the Children's IRB within 10 working days.

Any death occurring while a patient is in a study must be reported by phone to the Children's IRB within 24 hours and in writing within working five days.

Other SAEs **do not** need to be reported **if** the investigator has determined that the SAE is expected or due to the natural progression of the patient's underlying disease.

In times of doubt, for instance when at the time of the event it cannot be determined whether the SAE is a consequence of the study procedure, the SAE must be reported to the Children's IRB. If there is a clarification/change to any of the information initially submitted, provide a follow-up report.

Failure to report an occurrence in a timely manner may result in temporary or permanent suspension of the research study at the Children's site.

All correspondence with outside agencies (FDA, NIH, etc.) regarding adverse event reports are required to be submitted to the Children's IRB within 10 working days.

If the study sponsor requires you to submit an adverse event report to the Children's IRB, please note that it is your responsibility as the investigator to review any and all reports and ONLY forward to this office those adverse events that are both serious and unexpected and are judged to be related or possibly related to the study drug. If this is the case, you must complete and submit one SAE form for each individual safety report within five working days of receipt.

- } For more information see the Children's Policy 1.59—Research Adverse Event Reporting located on Careforce Connection <http://careforce/cms/default.aspx?id=2057>
- } See Children's Standard Operating Procedure: Serious Adverse Experience Reporting (Appendix K), Product Adverse Event/Device Malfunction Reporting (Appendix L)

25.0 Data Safety Monitoring

25.1 Data Safety Monitoring Boards

25.1 DATA SAFETY MONITORING BOARDS

Data and Safety Monitoring Plan (DSMP)
Data and Safety Monitoring Board (DSMB)(aka Data and Safety Monitoring Committee (DSMC))

- } See the Children's policy 1.57—Data and Safety Monitoring of Clinical Research Studies for more information.

Introduction

The IRB is responsible for determining if a study needs formal ongoing monitoring of data to ensure that research subjects will be protected. This responsibility stems from DHHS and FDA regulations stating a criterion for study approval be that "when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects" (45 CFR 46.111[a][6]). It is the responsibility of the PI to submit the data safety monitoring plan to the IRB.

All clinical trials require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the PI, Sponsor or program staff to a data and safety monitoring board (DSMB). These monitoring activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

The NIH requires investigators to submit a Data and Safety Monitoring Plan (DSMP) for clinical trials as part of the research application. A Data Safety Monitoring Plan is unique to the trial and should be commensurate with the potential risks and with the size and complexity of the trial. The plan is designed to ensure the safety of research subjects and the validity and integrity of the data and may include appointment of an independent DSMB.

Factors that suggest a Data Safety Monitoring Board (DSMB) is needed:

1. A large study population.
2. Multiple study sites. *It is more difficult to recognize a pattern of increased or unusual problems when investigators treat small fractions of the population separately.*
3. Highly toxic therapies or dangerous procedures.
4. High expected rates of morbidity or mortality in the study population.
5. High chance of early termination of the study.

DSMB

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. The DSMB will act in an advisory capacity to monitor patient safety and evaluate the efficacy of a research study. The initial responsibility of the DSMB will be to approve the initiation of a clinical trial. After this approval and at periodic intervals to be determined, usually twice annually or every six months during the course of the trial, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents and plans for data safety and monitoring.
2. Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome.
3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial.
4. Review clinical trial performance, make recommendations and assist in the resolution of problems reported by the PI.
5. Protect the safety of the study participants.
6. Report on the safety and progress of the trial.
7. Make recommendations to the Sponsor, the PI, and, if required, to the FDA concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study.
8. If appropriate, conduct interim analysis of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB.
9. Ensure the confidentiality of the trial data and the results of monitoring.
10. Assist the Sponsor by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

Membership

The DSMB consists of five voting members appointed for a fixed term by the PI or designee. Three members will constitute a quorum. Voting members should include physicians, statisticians, other scientists and lay representatives selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology. Members may be from within or outside the institution, but a majority should not be affiliated with the institution. Staffs affiliated with the institution who are members of the DSMB should view themselves as representing the interest of patients and not that of the institution. Membership consists of persons completely independent of the investigators who have no financial, scientific or other conflict of interest with the trial. Current or past collaborators or associates of the PI are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required. Those directly involved with the conceptual design or analysis of a particular trial must excuse themselves from all DSMB discussion of the particular trial and must not receive that portion of the DSMB report related to the particular trial.

The Chair of the DSMB will be selected from among the voting members. The chairperson is responsible for overseeing the meetings, developing the agenda in consultation with the Sponsor and the PI. The chair is the contact person for the DSMB. The Sponsor will serve as ex-officio member.

A safety officer will be identified at the first meeting. This person will be the contact person for severe adverse event reporting. Procedures for this will be discussed at the first meeting.

Conflict of Interest

DSMB members are subject to the awardee's policies regarding standards of conduct. Individuals invited to serve on the DSMB as either voting or nonvoting members will disclose any potential conflicts of interest, whether real or perceived, to the trial PI and the appropriate institutional official(s), in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts which develop during a member's DSMB tenure must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution's policies.

Board Process

The first meeting will take place face-to-face before initiation of the trial to discuss the protocol, approve the commencement of the trial, and to establish guidelines to monitor the study. The Sponsor and PI will prepare the agenda to address the review of manual of operating procedures, initiation of the trial, identification of a safety officer, reporting of adverse events, stopping rules, interim analysis plan, etc.

Meetings of the DSMB occur two times a year at the call of the Chair. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the PI and members of his/her staff.

Meetings may be convened as conference calls as well as in person, although the initial meeting and meetings to discuss interim analysis will be face-to-face. An emergency meeting of the DSMB may be called at any time by the Chairperson or Sponsor should questions of patient safety arise.

Meeting Format

An appropriate format for DSMB meetings consists of an open and a closed session. The open sessions may be attended by the PI, institution staff and Sponsor, but should always include the study biostatistician. Issues discussed at open sessions will include conduct and progress of the study, including patient accrual, compliance with protocol and problems encountered. Patient-specific data and treatment group data may not be presented in the open session.

The closed session will be attended only by voting DSMB members. Others may be requested to attend by the DSMB (e.g., study statistician). All safety and efficacy data are, and must be, presented at this session. The discussion at the closed session is completely confidential.

Should the DSMB decide to issue a termination recommendation, full vote of the DSMB is required. In the event of a split vote, majority vote will rule and a minority report should be appended.

Reports

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the coordinating center/statistical office, trial investigator(s), National Cancer Institute (NCI) program staff and statisticians and individual DSMB members to ensure that the DSMB is kept apprised of nonconfidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

Interim reports are generally prepared by the study statistician(s) and distributed to the DSMB at least 10 days prior to a scheduled meeting. The contents of the report are determined by the DSMB. Interim data reports generally consist of two parts. Part one (Open Session Report) provides information on study aspects such as accrual, baseline characteristics and other general information on study status. Part two (Closed Session Report) may contain data on study outcomes, including safety data and depending on the study, perhaps efficacy data. The Closed Session Report is considered confidential. Copies distributed prior to and during a meeting are collected by the study statistician(s) following the meeting. Data files to be used for interim analyses should have undergone editing and quality control procedures.

A formal report (meeting minutes) from the Chair will be sent to the full DSMB within three weeks of the meeting. Once approved by the DSMB, the Chair will forward the approved minutes to the Sponsor and the PI within six weeks of each meeting.

Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The Chair should transmit such a recommendation to the Sponsor as rapidly as possible. The

Sponsor would then notify the PI. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, etc. If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision.

Mailings to the DSMB: On a scheduled basis (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members or to the designated safety officer (to be determined at the first meeting). Any concerns noted should be brought to the attention of the Chair or designated safety officer who will take appropriate action.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

Submit the most recent DSMB report to the IRB as soon as it becomes available. Keep and file any additional correspondence (e.g., e-mails, letters, meeting minutes) with the DSMB and its members.

Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. Each member of the DSMB, including nonvoting members, must sign a statement of confidentiality.

} For more details see the Appendix M—Policy of the National Cancer Institute For Data And Safety Monitoring of Clinical Trials.

Resources for Guidance on DSM

General Clinical Research Center (GCRC)—[Data and Safety Monitoring](#)

University of Minnesota Cancer Center—[Data and Safety Monitoring Plan](#) (University of Minnesota IRB reviewed and approved Oct. 23, 2001)

National Cancer Institute

[Data and Safety Monitoring Guidelines](#)

[Data and Safety Monitoring Example Plans](#)

National Institutes of Health

(Draft) [Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees](#)
November 2001

[Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials](#)
June 5, 2000

[NIH Policy for Data and Safety Monitoring](#)
June 10, 1998

26.0 Protocol Modifications

- 26.1 Protocol Amendments
 - 26.2 Protocol Deviations and Violations
 - 26.3 Premature Discontinuation of a Study
-

26.1 PROTOCOL AMENDMENTS

When seeking a modification to an approved clinical trial you must consider the following rules:

- Any modification to an approved trial and/or revision to an approved informed consent form must be approved by the IRB before the PI can institute the changes.
- Modifications are ANY changes, updates or correspondence relating to an approved research protocol and include, but not limited to, any of the following issues:
 - Amendment(s) to the original protocol. When a Sponsor or Investigator (if Investigator initiated) amends an existing protocol, the Sponsor sends supporting documentation for the amendment. Amendments are usually numbered and dated by the Sponsor.
 - Addition of new procedures or tests.
 - Deletion of procedures or tests.
 - Changes of study staff such as: PI, CRC
 - Contact information changes
 - Adding a new site(s) or deleting a site(s)
 - Change in enrollment (increase number, decrease number or total to be enrolled.)
 - Changes to the informed consent form (IFC).
 - Changes to advertisements.
 - Investigator's Brochure changes
 - Addition or deletion of a funding source.

26.2 PROTOCOL DEVIATIONS AND VIOLATIONS

Adherence to the clinical protocol is of critical importance. Failure to follow the protocol exactly is a violation of FDA regulations, the Clinical Trial Agreement, and GCP, and is potentially dangerous to trial subjects. The Investigator must not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects. An Investigator who changes the protocol to eliminate a hazard must immediately notify the IRB and the Sponsor of the change and the reasons for the change.

The International Conference on Harmonization (ICH) Guidance E6 Good Clinical Practice elaborates upon these Investigator responsibilities in section 4.5

4.5.2 The Investigator must not implement any deviation from, or changes of, the protocol without agreement by the Sponsor and prior review and documented approval for the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), change of telephone number(s)).

4.5.3 The Investigator, or person designated by the Investigator, must document and explain any deviation from the approved protocol.

4.5.4 The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the:

- a. IRB for review and approval/reporting, as required.
- b. Sponsor for agreement and, if applicable
- c. Regulatory authority(ies)

26.3 PREMATURE DISCONTINUATION OF A STUDY

If a trial is terminated prematurely or suspended, the Sponsor should promptly inform the investigators of the termination or suspension and the reason for the termination or suspension. The PI is responsible for notifying the institution and IRB. The institution and IRB should be provided the reasons for the termination or suspension by the Investigator, as specified by the applicable regulatory requirement(s).

If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the Sponsor and the IRB and should provide the Sponsor and the IRB a detailed written explanation of the termination or suspension.

If the IRB terminates or suspends a trial, the Investigator should inform the institution and the Sponsor. The Investigator should provide the Sponsor with all required reports and provide the IRB with a summary of the trials outcome.

- } See Children's Standard Operating Procedure—Managing Protocol Amendments (Appendix N)

27.0 Continuing Review/Renewal

27.1 IRB Continuing Reviews

27.1 IRB CONTINUING REVIEWS

The investigator is responsible for submitting annual or bi-annual reviews of the study, depending on the risk to subjects as determined by the IRB. Documentation to be submitted is defined by the IRB in Policy 1.16—Institutional Review Board Standard Operating Procedures located on Careforce Connection: <http://careforce/cms/default.aspx?id=2057>

28.0 Financial Accounting: Post-award Process

- 28.1 Coordinating the Project
 - 28.2 Patient Care Invoicing
 - 28.3 Grants Accounting at Children's
 - 28.4 Process for Payment by Sponsors
 - 28.5 Grants Accounting at Emory
-

Financial Accounting: Post-award Process

The post-award process begins when the pre-award process is completed, the funds are available, and the PI has received the notice of award. Post-award activities, coordinated and managed through the Office of Grants Accounting and Contracts, include:

1. Coordinating the project
2. Patient care invoicing
3. Grants accounting

28.1 COORDINATING THE PROJECT

The research coordinator/nurse will meet with the Office of Grants Accounting and Contracts staff to review the project and setup overall coordination of the project.

28.2 PATIENT CARE INVOICING

- An important issue of research patient care procedures is ensuring that the patients and/or their insurance is not billed.
- The Office of Grants Accounting and Contracts has to be informed when these procedures have been performed. There is no internal trigger that alerts the office that a research patient has had a research visit.

- Charges are posted to the patient account by multiple people through the hospital.
- The Office of Grants Accounting and Contracts has to monitor all patient accounts to ensure the patient/insurance is not billed.
- To ensure study–related patient care activities are billed accurately, the Office of Grants Accounting and Contracts will create a research account within the Children’s Patient Accounting System—SMS. This research account is used internally and is managed by the Office of Grants Accounting and Contracts staff. A separate account is created for every study at each campus. Therefore, if the same study is being conducted at both hospitals, a separate account is created at each location. Clinical research coordinators will be provided the study account number for use in all communications.
- It is the coordinators responsibility to ensure that the Office of Grants Accounting and Contracts has the information by:
 - Preregistration process
 - Notification of appointment date if not preregistered
 - Completing the Patient Tracker after each visit whether the patient is preregistered or not. The completed Patient Tracker must be e-mailed to the staff in the Office of Grants Accounting and Contracts. The Patient Tracker is available on the Children’s public Web site at www.choa.org and Careforce Connection. The office of Grants and Accounting provides the Patient Tracker for each study.
- The Office of Grants Accounting and Contracts internally tracks these charges for each study and invoices the Coordinator.
- The Coordinator approves and processes for payment.
- Invoices for Emory projects are processed through Emory for payment. Emory mails a check to the Office of Grants Accounting and Contracts, this office processes the check through the Children’s Corporate Finance department.
- Invoices for private practice are paid by check to Children’s and mailed to the Office of Grants Accounting and Contracts, this office processes the check through the Children’s Corporate Finance department.
- Invoices for the Children’s projects are processed internally. The Coordinator returns the approved invoice to the Office of Grants Accounting and Contracts. This office processes the invoice internally and expenses the Children’s activity or study grant activity account.

28.3 GRANTS ACCOUNTING AT CHILDREN’S

- The costs of conducting the project are expensed to the grant activity number.
- The Research Coordinator (or Nurse/Manager) processes paperwork for expenses through the Office of Grants Accounting and Contracts either for approval or tracking purposes.
- The Office of Grants Accounting and Contracts ensures that expenses are allowable by funding source.

28.4 PROCESS FOR PAYMENT SPONSORS

- Payment is made by the Sponsor in a variety of ways and could include:
 - Sponsor pays as work is completed and received.
 - Children’s invoices Sponsor.
 - Children’s invoices Emory for all subcontracts.

- Payment from sponsor/funding source is received by the Office of Grants Accounting and Contracts and is processed to the Children's Corporate Finance department.
- Direct costs are deposited to grant activity account.
- Indirect costs are deposited to a separate account at Children's.
- Monthly financial reports are received and reviewed for accuracy by the Office of Grants Accounting and Contracts.
- Monthly financial reports are forwarded to the PI, Coordinator or Manager.
- After the study is complete and all expenses have been paid, grant activity is closed.

28.5 GRANTS ACCOUNTING AT EMORY

- Grants administered by Emory are managed at the departmental level.
- The Children's subcontracts with Emory are included as Direct Costs in Emory budgets.
- Children's creates a grant activity account for each study.
- Children's charges expenses incurred by Children's to the grant activity account.
- Children's invoices Emory University Department for expenses posted to the Children's grant activity account.
- The Children's Office of Grants Accounting and Contracts collaborates with either the Study Coordinator or the Research Manager to create an invoice.
- Checks are received in the Office of Grants Accounting and Contracts and processed for deposit to the grant activity account.

29.0 Audits

- 29.1 Audit Procedures
- 29.2 Audit Areas
- 29.3 Common Deficiencies

29.1 AUDIT PROCEDURES

The objective of the Quality Monitoring program for Human Subjects Research is to:

- Provide a systematic means to evaluate compliance with regulations and to assure human subjects protections
- Improve compliance with regulations and assure subject protection
- Provide feedback to the PI and/or IRB, as needed, to assure compliance
- Provide education to the PI and/or IRB as needed.

1. Random review for quality assurance

- a. **Scheduled**—This type of review is considered a full review. Focus of review includes roles and responsibilities of research team members, regulatory and IRB compliance, consent form elements, recruitment, eligibility and consenting process, case review for protocol adherence,

source documentation and data collection, adverse events, file security, pharmacy operations and other suitable aspects of the study.

- b. **Unscheduled**—A mini-review to evaluate a study file for regulatory documents, protocol version in use, recent AE submissions and modifications, informed consent documentation, and data confidentiality and file security.
2. **Informed consent review**—This type of review is intended to support researchers in assuring that adequate informed consent is provided to human subjects participating in their trials. This type of review may include observation (when possible) of the consenting process; verification that the person consenting the subject is qualified and designated by PI; review of the consent form for valid date, signatures and date; documentation of consent, and confirmation that a copy was given to subject; and review of the consent form for basic elements of consent according to the Common Rule.
3. **For cause review**—This is performed when concerns regarding compliance, protocol adherence or subject safety are brought to the attention of the IRB or Research Compliance Office. This is considered a full review.

Written notification of pending review will be sent from the Manager of Research Compliance. It is the responsibility of the Research Compliance Monitor to schedule the visit after receiving notice.

The following is an estimate of the timeframe for notification depending on the type of review being employed:

1. **Random reviews** will be scheduled two weeks in advance; however unscheduled mini-reviews may be performed without notice.
2. **Consent reviews** may be scheduled by mutual convenience when it involves the observing the consenting process, otherwise, when limited to chart review; there will be two weeks notice.
3. **For cause reviews** may be scheduled with 24 hours notice or without notice if there is concern for safety of human subjects.

29.2 AUDIT AREAS

REVIEW ACTIVITIES MAY INCLUDE:

1. **IRB Process**
 - Dates of approval and start of research
 - Changes in protocol
 - Progress reports
2. **Protocol and Consent Process**
3. **Records Regarding Subjects**
 - Eligibility criteria

- Informed consent
- Reporting of AE
- Subject accrual
- Data collection tools/procedures

4. **Test Article Accountability**

- Site of storage
- Inventory records
- Procedures for documenting transactions

5. **Subjects**

- Availability of subjects
- Confirmation of eligibility and adherence to protocol
- Reporting on dropouts and AE
- Follow-up of subjects (and AE) after conclusion of study

6. **Lab Tests**

- Site and quality of performance

7. **Documentation**

- Research records
- Clinic/medical records
- Regulatory file
- All related study correspondence

29.3 COMMON DEFICIENCIES

- Protocol never approved by IRB.
- Initial IRB approval documentation missing.
- Registration and/or treatment of patient prior to full IRB approval.
- Registration of patient on protocol during lapse in IRB approval.
- No continuing IRB approval.
- Reportable AE not reported to IRB.
- Lack of documentation of IRB approval of a protocol amendment
- Omissions of one or more of the elements required by federal regulations.
- Omissions of multiple risks/side effects as listed in the protocol.
- Outdated consent forms.

} See the Children’s Standard Operating Procedure—Handling Sponsor, Quality Assurance (QA) or IRB-initiated Audits for more information (Appendix O)

Section IV Subject Management

30.0 Screening

- 30.1 Gathering Information
- 30.2 Documentation

Screening Tests Prior to Study Enrollment

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. This allows an investigator to discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining consent. Informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out). When wash-out is done in anticipation of, or in preparation for, the research, it is part of the research.

Procedures that are to be performed as standard of care and would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition may be performed and the results subsequently used for determining study eligibility without first obtaining consent. Alternatively, informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Clinical screening procedures for research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure [21 CFR 56.102(i)], the IRB may choose to use expedited review procedures [21 CFR 56.110]. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

Certain clinical tests, such as for HIV infection, may have state requirements regarding (1) the information that must be provided to the participant, (2) which organizations have access to the test results and (3) whether a positive result has to be reported to the health department. Prospective subjects should be informed of any such requirements and how an unfavorable test result could affect employment or insurance before the test is conducted. The IRB may wish to confirm that such tests are required by the protocol of the study.

30.1 GATHERING INFORMATION

During the screening process information should be gathered to determine subject eligibility for the trial. The majority of clinical trials utilize a case report form to gather and record this data.

- Review the inclusion/exclusion criteria detailed in the protocol and assess if the subjects meet all inclusion criteria for enrollment (assuming HIPPA waiver for screening).
- Gather and record relevant laboratory data and patient medical information.
- Assess for any confounding factors that would limit the subject's ability to complete all trial visits or expectations such as travel distance for any follow-up visits or subject's custody situation.
- For hospitalized patients, it is also helpful to discuss your screening activities and possible intentions to enroll with the patient's primary physician who is managing the hospitalization. This collaborative effort can help to determine if there are any additional obstacles to enrollment.

30.2 DOCUMENTATION

Screening documentation begins with annotating the informed consent process has been completed, and the subject has agreed to participate in the study by signing the informed consent before any study procedures have been initiated. Screening procedures are completed as written in the protocol. Some routine screening procedures include (but not limited to) lab work, physical exams, medical and concomitant medication history and vital signs. All of these are assessed and obtained to ensure subject safety that all inclusion criteria have been met and no exclusion criteria. Screening documentation is inclusive of the subject's demographic information, completion of the informed consent process, and all protocol required screening procedures and assessments. Once test results are available, these outcomes become a part of the subject's screening documentation. Screening documentation is sufficient once completion of screening procedures criteria progresses the subject to the enrollment phase of the study.

31.0 *Consenting*

- 31.1 Underlying Principles
 - 31.2 Obtaining Informed Consent
 - 31.3 Reconsenting
-

31.1 UNDERLYING PRINCIPLES

The History of Informed Consent and the System of Protections

During the past half-century, the international and U.S. medical communities have taken numerous steps to protect people who take part in clinical research. The following timeline provides an overview of some of the key events that have contributed to the development of the current system.

1947—The Nuremberg Code

Developed in response to the Nuremberg Trials of Nazi doctors who performed unethical experimentation during World War II, the Code was the first major international document to provide guidelines on research ethics. It made voluntary consent a requirement in clinical research studies, emphasizing that consent can be voluntary only if participants:

- Are able to consent
- Are free from coercion (i.e., outside pressure)
- Comprehend the risks and benefits involved

The Code also states that researchers should minimize risk and harm, make sure that risks do not significantly outweigh potential benefits, use appropriate study designs and guarantee participants' freedom to withdraw at any time. The Nuremberg Code was adopted by the United Nations General Assembly in 1948.

1964—Declaration of Helsinki

At the 18th World Medical Assembly in Helsinki, Finland, the World Medical Association adopted 12 principles to guide physicians on ethical considerations related to biomedical research. It emphasizes the distinction between medical care that directly benefits the patient and research that may or may not provide direct benefit. These guidelines were revised at subsequent meetings in 1975 (Tokyo, Japan), 1983 (Venice, Italy) and 1989 (Hong Kong, China).

1974—The National Research Act

The U.S. Congress signed this act into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission was charged with:

1. Identifying the basic ethical principles that should govern medical research involving people
2. Recommending steps to improve the Regulations for the Protection of Human Subjects

1979—The Belmont Report

After four years of work, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The report sets forth three principles underlying the ethical conduct of research:

1. Respect for persons: recognizing the autonomy and dignity of individuals, and the need to protect those with diminished autonomy (i.e., impaired decision-making skills), such as children, the aged and the disabled
2. Beneficence: an obligation to protect persons from harm by maximizing benefits and minimizing risks
3. Justice: fair distribution of the benefits and burdens of research

The Belmont Report explains how these apply to research practices; for example, it identifies informed consent as a process that is essential to the principle of respect. In response to the report, both the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration revised their regulations on research studies that involve people.

1991—Federal Policy for the Protection of Human Subjects

This policy was adopted to ensure a uniform system of protections in all federal agencies and departments that conduct research.

31.2 OBTAINING INFORMED CONSENT

The process of obtaining informed consent must comply with the requirements of 45 CFR 46.116 and 21 CFR 50.25. The documentation of informed consent must comply with 45 CFR 46.117 and 21 CFR 50.27. The following comments may help in the development of an approach and proposed language by investigators for obtaining consent and its approval by IRBs:

- Informed consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is a fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand. Therefore, informed consent language and its documentation (especially explanation of the study's purpose, duration, experimental procedures, alternatives, risks and benefits) must be written in eighth-grade language, (i.e. understandable to the people being asked to participate). The written presentation of information is used to document the basis for consent and for the subjects' future reference. The consent document should be revised when deficiencies are noted or when additional information will improve the consent process.
- Use of the first person (e.g., "I understand that ...") can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence to a subject. Use of scientific jargon and legalese is not appropriate. Think of the document primarily as a teaching tool not as a legal instrument.
- Describe the overall experience that will be encountered. Explain the research

- activity, how it is experimental (e.g., a new drug, extra tests, separate research records, or nonstandard means of management, such as flipping a coin for random assignment or other design issues). Inform the human subjects of the reasonably foreseeable harms, discomforts, inconvenience and risks that are associated with the research activity. If additional risks are identified during the course of the research, the consent process and documentation will require revisions to inform subjects as they are recontacted or newly contacted.
- Describe the benefits that subjects may reasonably expect to encounter. There may be none other than a sense of helping the public at-large. If payment is given to defray the incurred expense for participation, it must not be coercive in amount or method of distribution.
 - Describe any alternatives to participating in the research project. For example, in drug studies the medication(s) may be available through their family doctor or clinic without the need to volunteer for the research activity.
 - The regulations insist that the subjects be told the extent to which their personally identifiable private information will be in confidence. For example, some studies require disclosure of information to other parties. Some studies inherently are in need of a certificate of confidentiality which protects the Investigator from involuntary release (e.g., subpoena) of the names or other identifying characteristics of research subjects. The IRB will determine the level of adequate requirements for confidentiality in light of its mandate to ensure minimization of risk and determination that the residual risks warrant involvement of subjects.
 - If research-related injury (i.e. physical, psychological, social, financial or otherwise) is possible in research that is more than minimal risk (see 45 CFR 46.102[g]), an explanation must be given of whatever voluntary compensation and treatment will be provided. Note that the regulations do not limit injury to physical injury. This is a common misinterpretation.
 - The regulations prohibit waiving or appearing to waive any legal rights of subjects. Therefore, for example, consent language must be carefully selected that deals with what the institution is voluntarily willing to do under circumstances, such as providing for compensation beyond the provision of immediate or therapeutic intervention in response to a research-related injury. In short, subjects should not be given the impression that they have agreed to and are without recourse to seek satisfaction beyond the institution's voluntarily chosen limits.
 - The regulations provide for the identification of contact persons who would be knowledgeable to answer subjects' questions about the research, rights as a research subject and research-related injuries. These three areas must be explicitly stated and addressed in the consent process and documentation. Furthermore, a single person is not likely to be appropriate to answer questions in all areas. This is because of potential conflicts of interest or the appearance of such. Questions about the research are frequently best answered by the investigator(s). However, questions about the rights of research subjects or research-related injuries (where applicable) may best be referred to those not on the research team. These questions could be addressed to the IRB, an ombudsman, an ethics committee or other informed administrative body. Therefore, each consent document can be expected to have at least two names with local telephone numbers for contacts to answer questions in these specified

areas.

- The statement regarding voluntary participation and the right to withdraw at any time can be taken almost verbatim from the regulations (45 CFR 46.116[a][8]). It is important not to overlook the need to point out that no penalty or loss of benefits will occur as a result of both not participating and withdrawing at any time. It is equally important to alert potential subjects to any foreseeable consequences to them should they unilaterally withdraw while dependent on some intervention to maintain normal function.

31.3 RECONSENTING

During the course of conducting a research study, investigators may find that changes to the protocol are indicated, whether due to newly discovered risks, a change in protocol design or some other factor. Whatever the change, it may require re-obtaining consent from previously consented subjects in order to continue their participation in the study.

The need to re-consent derives from the federal regulations governing research, which require that subjects be informed of significant new information that may affect their continued willingness to participate. This new information may include the following:

- Increase in study length
- Increased number of study visits
- A change in study venue(s)
- Increased risks to subjects
- Decreased benefit to subjects than previously believed to be present

Therefore, investigators should evaluate the need for re-consenting previously enrolled subjects when such types of changes occur.

32.0 *Enrollment*

32.1 Implementation

32.2 Documentation

32.3 Tracking

32.1 IMPLEMENTATION

Enrollment of a patient into a study includes specific steps that are taken to begin the study, and will be done according to the study protocol. Once a potential patient has been consented to participate in the study, has completed the screening process and it has been determined that the patient qualifies for study participation, the patient will then be enrolled into the study. After the enrollment point of the study, the patient enters the

study design, which may include randomization to a certain study procedure or the start of a study procedure that is being researched.

32.2 DOCUMENTATION

Documentation of patient enrollment is necessary in conducting research, and can include showing that the patient has undergone the screening process appropriately, and has met all inclusion criteria and no exclusion criteria. If patients are randomized into certain procedure groups, this must be documented as well.

32.3 TRACKING

Patient enrollment tracking should occur throughout the study duration. This tracking should include the patient's identification information, the date the patient was enrolled, any study assignment information (i.e.: randomization number) and other information pertinent to the patient's enrollment. Enrollment tracking logs are sometimes necessary to maintain and to send in to the Sponsor on a sponsored trial in order to communicate enrollment progress between the sites and the Sponsor.

33.0 Study Procedures

- 33.1 Subject File
 - 33.2 Registering/Scheduling Procedures
 - 33.3 Conducting Visits
 - 33.4 Payment Procedures
 - 33.5 Accessing Medical Records
-

33.1 SUBJECT FILE

PATIENT DOCUMENTS

The case report form (CRF) documents are all the information required by the protocol for each trial patient. Data recorded in the CRFs will originate from data that is originally captured on the source documents. The data recorded in CRFs will undergo statistical analysis, and after the study will form the basis for the study report. Therefore, it is vital that these forms are filled in correctly and completely. Omissions and errors can render data unfit for inclusion in the trials' statistical analyses; they can also delay reporting of the trial results. Some data in the case report forms could be considered source data (protocol-specific-data). For example, multiple blood pressure readings recorded directly on the CRFs to avoid transfer errors.

Study records which include both case report forms and documents that support data in those forms (these documents include source documents and applicable medical records), should contain: (1) basic subject identification information; (2) information showing that each subject meets the subject selection criteria or justification for otherwise enrolling the subject; (3) sufficient information to support data in the case report form as submitted to the sponsor; (4) information on each subjects exposure to

the test or control article, including the date (and time, if relevant) of each administration and the quantity administered; and (5) copies of case report forms should be retrievable in such a fashion that all information regarding each individual in a study is attributable to that individual.

Study records also include information obtained from tests and examinations, such as physical examinations; lab results; X-rays; progress notes; consultations; correspondence; information and data on the subject's condition before, during and after the clinical investigation; all diagnostic tests results; diagnoses made; concomitant or concurrent therapy.

To substantiate that each subject meets the subject selection criteria, records should be maintained, including the subject's medical history.

When FDA needs to verify the validity and completeness of the case report data submitted to the agency, FDA may audit study records in the possession of the Investigator or Investigator's institution. [21CFR 312.68 and 812.145].

33.2 REGISTERING/SCHEDULING PROCEDURES

Most protocols require that trial subjects be examined at specified time intervals and broken down in visit numbers; such as visit one at four weeks. It is very important that subjects are examined on the dates required within the protocol-specified time intervals, especially in drug/device studies. Often this is when efficacy and/or safety of research drugs or devices are evaluated. Also notification of any AEs that have taken place may be noted and reported within this timeframe. Visits that occur outside of the planned schedule are protocol deviations that can make interpretation of results difficult or impossible. Protocol deviations often require authorization/approval from a Sponsor and completion of the appropriate protocol deviation paperwork.

Every interaction with a subject is important. If during the trial, a subject visits your site for any reason, you must record that unscheduled visit and collect information as specified in the protocol. In addition, if the unscheduled visit is because of a suspected or certain AE, the corresponding AE or SAE documentation or report must be completed and submitted to the Sponsor/IRB within the required timeframe.

Each study will have a specified timeline to follow. This timeline may have a +/- window within the protocol requirements. The details of the visit are often stated in the consent form and outlined in the CRF for each patient. Often the requirements for each visit are listed in the timeline for the visit schedule. To improve compliance, coordinators can keep a tracking log which may also be utilized as an internal quality tool and as a reminder for upcoming patient appointments.

33.3 CONDUCTING VISITS

Study visits need to be conducted as stated in your approved protocol. Any altered visits such as missed or rescheduled visits need to be documented. Study visits are often scheduled for a specified time and area depending on type of study being done. The

types of procedures to be done at each study visit are also protocol-specific—refer to the protocol for the appropriate actions.

Outpatient research visits require preregistration. Go to [www.choa.org/Clinical Research](http://www.choa.org/Clinical_Research) to register patients. The ability to preregister requires an account setup by the office of Grants Accounting and Contracts during the pre-aware process. Often outpatient visits utilize a research request form for technical procedures and a patient tracking form for account management.

33.4 PAYMENT PROCEDURES

Payments or stipends may be made to research subjects for participation in research. These payments may be provided to reimburse the participant for the costs they incur as subjects. These costs may include travel, lodging and meals. With pediatric participants the costs most often includes the subject and their family. Sponsors will often include subject stipends in their study budget proposal or you can request this funding.

The amount and schedule of all payments should be included in the Informed Consent document and will be reviewed by the IRB at the time of initial review. The IRB will review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive nor present undue influence to participate. (21 CFR 50.20)

Payment to research subjects is not considered a benefit for study participation and should not be discussed in the benefit section of the informed consent. The payment amounts and payment schedule should be outlined in the section discussing the cost of being in the study.

Payments should occur as the study progresses and should not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or complete a phase of the study) had they not withdrawn. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.

33.5 ACCESSING MEDICAL RECORDS

To access medical records, a consent allowing release of the patients' records must be initially obtained. A medical records request can then be sent to the appropriate parties. The Children's release form is located on Careforce Connection under Health Information Services. Have the parent complete the Release of PHI side only.

For medical records accessibility within Children's, a chart pull request form needs to be completed. The form can be found on Careforce Connection under Health Information Services. When submitting the form to Medical Records enter as much patient information as possible. The patient's name, date of birth and the medical record are the key information to include on the chart request form. Allow a minimum of three days for your patients' charts to be pulled. Once they are ready, someone from Medical Records will e-mail or call you to let you know they are ready for review. In addition you will need to submit a copy of IRB approval along with the chart request form.

34.0 Subject Retention and Attrition

- 34.1 Retention Strategies
 - 34.2 Withdrawing a Subject
 - 34.3 Lost to Follow-up (LTF)
-

34.1 RETENTION STRATEGIES

Warning Signs for Potential Dropouts

- Other medical conditions placing patients at risk for being placed on confounding treatment
- Severe side effects
- Difficulty in initially tracking down subjects and/or missed appointments
- Distance necessary for travel to clinic
- Additional mental health symptoms and/or interpersonal difficulty

Retention Strategies

- Make reminder phone calls prior to appointment
- Schedule the interview at a time and place that is most comfortable for the participant
- Allow flexibility in scheduling appointments (i.e. evenings or weekends)
- Keep office visits short (no more than two hours, including lab work)
- Have a consistent contact person, providing incentives (i.e., free treatment, lunch pass, validated parking, monetary compensation)
- Spend increased amounts of time with the patient in the early phases of his/her study involvement
- Ensure patient that their information will remain confidential
- Maintain consistency in staff who are communicating with participants and collecting data
- Involve family to facilitate transportation to appointments

34.2 WITHDRAWING A SUBJECT

The statement regarding voluntary participation and the right to withdraw at any time can be taken almost verbatim from the regulations (45 CFR 46.116[a][8]). It is important not to overlook the need to point out that no penalty or loss of benefits will occur as a result of not participating or withdrawing at any time. It is equally important to alert potential subjects to any foreseeable consequences to them should they unilaterally withdraw while dependent on some intervention.

34.3 LOST TO FOLLOW-UP (LTF)

Once a patient has missed a scheduled study visit, the Study Coordinator will make an attempt to contact the study participant at all given contact numbers including those given for emergency purposes. Phone contacts will be attempted three times or until the subject is reached. These attempts will be documented in the subject's source documents with the time, date with details of the message left for the patient. If unsuccessful by the third attempt, a certified letter with signature confirmation will be sent to the subject's primary address. The letter will state the site is attempting to schedule a safety visit or final visit (if they have chosen to early discontinue the study). A copy of the certified letter becomes a part of the subject's source document.

35.0 *Managing Adverse Events*

35.1 Assessing Adverse Events (AE)

35.2 Clinical Management

35.1 ASSESSING ADVERSE EVENTS

The reporting period begins from the time of consent and ends as defined in the protocol. Refer to the protocol for specific guidelines. All AEs that occur in trial subjects during the AE reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered medication or product related. The protocol will describe procedures for dealing with AEs.

Ensure that the subject understands the importance of reporting anything untoward that happens to them while in a study. When discussing participation in a trial, make certain that patients are fully informed of all potential AEs. All clinical staff involved with the trial should be familiar with these procedures. The investigator makes the decision of grade of severity and relation of the AE. This is also protocol specific with reporting requirements to IRB and Sponsor as defined in protocol.

35.2 CLINICAL MANAGEMENT

When AEs are identified:

- Schedule subject for interim visit
- Treat subject as defined in protocol

Section V Study Closeout

36.0 Final Reconciliations

- 36.1 Reconciling Investigational Product Inventory
 - 36.2 Database Finalizations
-

36.1 RECONCILING INVESTIGATIONAL PRODUCT INVENTORY

- PI schedules meeting with Sponsor/Representative to meet with Investigational Pharmacy Service to conduct final inventory
- Record the accuracy of the inventory
- Log any discrepancies in a note to file
- Document the final disposition of the product (destroy on site or return to Sponsor)

36.2 DATABASE FINALIZATIONS

- Clarify questions for Sponsor once the database is satisfactorily locked
- For investigator-initiated studies, complete the data and quality assure the database
- Submit for analysis

37.0 Post-study Communication

- 37.1 Institutional Notifications
 - 37.2 Final Reports
-

37.1 INSTITUTIONAL NOTIFICATIONS

As the sample size is reached or follow-up visits and treatment is completed, the study is closed. There should be no further screening, enrollment or safety visits. Data collection and clarification should be complete. Correspondence from the Sponsor of the trial requesting the study close-out should be filed in the Regulatory binder and forwarded to the local IRB with a Termination of IRB Approval form. The IRB will respond with a letter acknowledging the request to terminate the study. The PI is responsible for:

- Notifying all services in the organization that are impacted (i.e. lab, pharmacy, etc.)
- Notifying Grants Accounting and Contracts office, if applicable.

37.2 FINAL REPORTS

Correspondence to the study participants should be generated to notify them to complete the last safety visits and of the study termination. Drug accountability should be completed. All used and unused drugs should be returned to the Sponsor or destroyed (per protocol). A note to file should be generated to address the duration of storage and location for source documents and clinical research forms (CRFs). Ensure a study termination request has been sent and acknowledged by your local IRB. Ensure there are no further screenings, enrollment, safety visits, data collection or clarification for this study. Some examples of these types of reports are:

- IRB Summary
- Sponsor Accountability Logs
- Grant—Final report to funding source

38.0 *Storage and Archiving*

38.1 Study Record Retention

38.2 Human Tissue Retention

38.1 STUDY RECORD RETENTION

1. Study site research records: The Children's study site research records for each project shall be retained for at least 10 years after termination of all research procedures. Children's, the study sponsor, and/or federal regulations may require longer retention of records for particular research. If the study documentation contains Protected Health Information (PHI) related to treatment that is not originated from the medical record, then the documentation/records shall be retained according to Policy 8.18 Document Retention and Destruction located in the policy section of this manual.
2. IRB research records: The IRB records for each study shall be retained for at least three years after termination of the IRB approval. Additional information regarding this requirement is located in Policy 1.16 located in the policy section of this manual.
3. Research Financial Records: Research Patient Care billing records are retained one year after the study ends. Grants Accounting files are retained indefinitely.
4. Research Compliance Records: The Research Compliance Records shall be retained for six years from the date materials are replaced or updated.

} Storage details may be found in the Children's policy 8.47 Research Record Storage, Retention, and Disposition of Documents/Records on the Clinical Research Web site: <http://careforce/cms/default.aspx?id=2057>.

38.2 HUMAN TISSUE RETENTION

Length of storage for human tissues is based on the opinion of the Biorepository Committee (committee consisting of physicians representing Pathology and various specialties within Children's) and is predefined in the protocol. The extent of and length of particular studies will also influence the length of storage for tissue samples.

39.0 *Publications and Presentations*

- 39.1 Publication Rights
 - 39.2 Responsible Authorship
 - 39.3 Journal Submission
 - 39.4 Poster Presentation
-

39.1 PUBLICATION RIGHTS

Copyrightable Works Children's does not assert its rights in academic or scholarly copyrightable work, such as books, articles, and creations, including work for hire, except under circumstances in which copyrightable works are either (a) related to the Children's personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise, or (b) made with the use of the Children's support, and were

- Specifically assigned and funded by Children's
- Developed with the use of substantially more support at Children's than is normally provided to the Children's personnel
- Developed under an externally funded agreement with Children's unless otherwise provided in the agreement.

39.2 RESPONSIBLE AUTHORSHIP

Children's has adopted the International Committee of Medical Journal Editors (ICMJE)—Uniform Requirements for Manuscripts Submitted to Biomedical Journals as a guideline for authorship and submission to medical journals. Please visit www.icmje.org for more information.

Who qualifies for authorship?

- Authorship credit should be based on three conditions, *all of which* must be met:
 - 1) Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data.
 - 2) Drafting the article or revising it critically for important intellectual content.
 - 3) Final approval of the version to be published.

- Acquisition of funding, general supervision of researchers/authors, or review and approval of a manuscript, by themselves, *do not* justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. At least one author, usually the first, should take responsibility for the integrity of the work as a whole, from inception to publication/distribution. Contributors who do not meet the criteria of authorship should be listed in an acknowledgements section. Those who might be acknowledged include a person who provided purely technical help, writing assistance or a department chair who provided only general support. Financial and material support should be acknowledged as well.

Determining Author Order

The order of authorship on the byline should be a joint decision of the coauthors. Author order should be discussed early and revised as needed. Authors should be prepared to explain the rationale for the order in which authors are listed. Please visit www.icmje.org for authorship guidelines for groups.

Author Roles and Responsibilities:

First Author: In addition to the criteria for authorship, first authors should consider the following additional responsibilities:

- Provide leadership for authorship team in determining author order, establish writing assignments and deadlines for written contributions and coauthor reviews, and ensure an open forum for coauthors to share concerns and suggestions.
- Compile drafts, distribute them for review, and provide specific direction for reviews and revisions.
- Ensure all ethical considerations (e.g. IRB review, disclosure of conflicts of interest) have been addressed.

Coauthors: Contributors to the development of an information product should participate in an initial decision about authorship and other contributions as soon as possible with relation to the development of the manuscript. Coauthors should participate in setting assignments and deadlines for written contributions and coauthor reviews. The authorship team should revise author order as necessary to reflect evolving contributions of team members.

39.3 JOURNAL SUBMISSION

Manuscript Preparation

It is recommended that potential observational and experimental journal articles are divided into sections with the headings Introduction, Materials and Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content. Case reports, reviews and editorial are likely to need other formats.

It is also recommended that all manuscripts are double spaced—including the title, page, abstract, text, acknowledgments, references, individual tables and legends—and generous margins to make it possible for editors to easily review and edit line by line. The same is true for electronic submissions as they may be printed for review. All pages should be numbered starting from the title page so that the editors and reviewers can refer to specific portions of the manuscript. Please visit www.icmje.org for detailed descriptions of content to be considered for inclusion in each section.

39.4 POSTER PRESENTATION

Children's is making it easier for you to produce effective poster presentations through the use of newly created templates available exclusively at Megabytes Digital. Children's will pay for the creation of your posters if you use one of the templates designed to include the following logos:

- Children's
- Children's and Emory University
- Aflac Cancer Center and Blood Disorders Service and Emory University
- Children's and Georgia Institute of Technology
- Children's and Morehouse School of Medicine

Direct billing has been established with Megabytes Digital. See Careforce Connection for specific contact information.

40.0 *Intellectual Property*

- 40.1 Definition
- 40.2 Categories of Intellectual Property
- 40.3 Intellectual Property Ownership at Children's
- 40.4 Intellectual Property Protection Mechanisms

40.1 DEFINITION

Intellectual Property is a creation of the intellect that has commercial value. It includes copyrighted property such as literary or artistic works, and ideological property, such as patents, titles of origin, business methods, as well as industrial processes. Intellectual property is a term often used to refer generically to property rights created through intellectual and/or discovery efforts of a creator that are generally protectable under patent, trademark, trade secret, trade dress or other law. The U.S. legal system developed the concept of intellectual property to encourage the creation of valuable ideas and protect them from being stolen.

40.2 CATEGORIES OF INTELLECTUAL PROPERTY

Common types of intellectual property rights protect different types of abstract subject matter. The five main types of nonphysical things considered to comprise intellectual property are:

- **Copyright/©:** A copyright protects original works of authorship fixed in a physical medium of expression. Copyrights can include published and unpublished works—literary, dramatic, and musical and dance compositions, films, photographs, and audiovisual works, paintings, sculpture, and other visual works of art, as well as computer programs—from being copied.
- **Patent:** A patent is a grant issued by the federal government giving an inventor the right to exclude others from making, having made, using, leasing, offering to sell, selling, or importing an invention in the United States. A patent does not necessarily guarantee inventors the right to make, use or sell their inventions; in some cases, utilizing a patented invention depends on another person's prior, unexplored patent.
- **Trademark™ and Registered Service Marks ®:** Trademark and registered service mark protection covers a nonfunctional word, logo, slogan, symbol, design—or any combinations of these—that distinguishes a product or service. Essentially trademarks are the brand names that promote competition by giving products corporate identity and marketing leverage.
- **Trade Secret:** A trade secret is a formula, pattern, manufacturing process, method of doing business, or technical know-how that gives its owner a competitive advantage. Trade secrets cover a wide range of information, including chemical compounds, machine patterns, customer lists and software.
- **Designs:** Intellectual property of design refers to the form of appearance, style or design of an industrial object, for example furniture or textiles.

40.3 INTELLECTUAL PROPERTY OWNERSHIP AT CHILDREN'S

- } Please refer to the Children's Intellectual Property Policy 1.51—located in the policy section of the Clinical Research Web site on Careforce Connection:
<http://careforce/cms/default.aspx?id=2057>

Children's will own all copyrightable, patentable, registered, claimed or other intellectual property created or developed by the Children's personnel if the intellectual property either (a) is related to the Children's personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise or (b) was made with the use of the Children's resources or support.

40.4 INTELLECTUAL PROPERTY PROTECTION MECHANISMS

Children's has established an intellectual property policy to support research and development of commercially valuable works. The policy is intended to encourage, support, reward and recognize the rights and interests of the Contributors and Sponsor(s).

The Children's personnel will promptly disclose the existence of any intellectual property (that is, intellectual property to which Children's may assert ownership rights) to the Office of General Counsel (OGC). Delay in contacting the OGC may compromise the ability to secure effective legal protection for intellectual property. Publication or presentation of research results prior to filing a patent application may

substantially compromise patent protection both in the U.S. and in foreign countries. Prompt disclosure is also necessary to ensure that the appropriate Research Sponsor is notified in a timely manner and that Children's is in compliance with the federal laws governing research or regulating the Sponsor.

How can you protect your intellectual property?

- Know what you have. If you understand what needs to be protected, you can better understand how to protect it and whom to protect it from. To adequately protect intellectual property, Investigators must communicate on a regular basis with the Director of Clinical Research and OGC.
- Label it. If information is confidential, put a label on it that says so. If your data is proprietary, put a note to that effect on every log-on screen and password protect all information. If you must try to prove that a person took information they were not authorized to take, your argument will not be valid if you cannot prove the information was clearly protected.
- Lock it up. Physical and digital protection is a must. Lock the rooms where sensitive data is stored; whether it is the electronic storage facility or the file room where paper copies are kept. Keep track of who has keys, use passwords and limit employee access to sensitive databases. Contact IS&T for assistance in protecting your electronic data.
- Look at the whole. Intellectual property protection requires communication between all corporate functions. Someone could access your information in many different ways that seem accidental.

Appendix A

INVESTIGATIONAL NEW DRUG (IND) APPLICATION PROCESS

- Introduction
- Pre-IND Consultation Program
- Guidance Documents for INDs
- CDER Investigational New Drug (IND) Renumbering
- Information for Clinical Investigators
 - Institutional Review Boards and Protection of Human Subjects in Clinical Trials
 - Federal Regulations for Clinical Investigators
- Laws, Regulations, Policies and Procedures
 - *Code of Federal Regulations*
 - Manual of Policies and Procedures (MaPPs)
- IND Forms and Instructions (FDA 1571 and FDA 1572)
- Emergency Use of an Investigational Drug or Biologic
- Drug Development and Review Definitions
- Frequently Asked Questions on Drug Development and Investigational New Drug Applications
- Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting
- Organization, Contact and Meeting Information
- Related Topics

Introduction

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies—Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information—Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information—Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators—professionals (generally physicians) who oversee the administration of the experimental compound—to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.


Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

This interactive chart summarizes the IND process, including how CDER determines if the product is suitable for use in clinical trials.

This information is designed for individuals from pharmaceutical companies, government agencies, academic institutions, private organizations, or other organizations interested in bringing a new drug to market. Each of the sections below contains information from CDER to assist you in the IND application process. For specific information, click on a link to go directly to a section or Web page.


Resources for IND Applications

The following resources have been gathered to provide you with the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures.

Pre-IND Consultation Program: CDER offers a Pre-Investigational New Drug Application (IND) Consultation Program to foster early communications between sponsors and new drug review divisions in order to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class and can each be contacted using the designated Pre-IND Consultation List.  (12/5/2006)


Guidance Documents for INDs

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office.

For the complete list of CDER guidances, please see the Guidance Index. Most of these documents are in Adobe Acrobat format , also known as PDF. The free upgrade to Adobe Acrobat 3.0 or higher is recommended, especially if you have difficulty opening any of the documents below. For information on a specific guidance document, please contact the originating office.

Guidance documents to help prepare INDs include:

- Guidance for Industry: INDs—Approaches to Complying with CGMPs for Phase 1 Drugs (Draft) [HTML] or [PDF] (1/12/2006)
- Guidance for Industry: Exploratory IND Studies [HTML] or [PDF] (1/12/2006)

- Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs Including Well Characterized, Therapeutic, Biotechnology-Derived Products.  Provides description of required sections of an application.
- Q & A—Content and Format of INDs for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products. Optional Format: PDF. This guidance is intended to clarify when sponsors should submit final, quality-assured toxicology reports and/or update the Agency on any changes in findings since submission of non-quality-assured reports or reports based on non-quality-assured data. (Issued 10/00).
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. Optional Format: PDF (Issued 10/2000, Posted 10/27/2000). This guidance should be useful for applicants planning to conduct bioavailability (BA) and bioequivalence (BE) studies during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs.
- IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer. (1/2004)
- Drug Master Files. A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- Required Specifications for FDA's IND, NDA, and ANDA Drug Master File Binders.
- Immunotoxicology Evaluation of Investigational New Drugs [PDF] (Issued 10/2002, Posted 10/31/2002). This guidance makes recommendations to sponsors of investigational new drugs (INDs) on (1) the parameters that should be routinely assessed in toxicology studies to determine effects of a drug on immune function, (2) when additional immunotoxicity studies should be conducted, and (3) when additional mechanistic information could help characterize the significance of a given drug's effect on the immune system.

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. With numerous amendments it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations (CFR)






Code Of Federal Regulations (CFR). The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles that represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* and related statutes. Section 21 of the *CFR* contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.


- The following regulations apply to the IND application process:

21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

Manual of Policies and Procedures (MaPPs)




CDER's Manual of Policies and Procedures (MaPPs). MaPPs are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures. MaPPs of particular interest to IND sponsors include:

- 4200.1  Consulting the Controlled Substance Staff on INDs and Protocols That Use Schedule I Controlled Substances and Drugs (Issued 5/8/2003)
- 5210.5  Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
- 6030.1 IND Process and Review Procedures (Including Clinical Holds).  Includes general IND review principles, policies and procedures for issuing clinical holds of INDs, and processing and responding to sponsors' complete responses to clinical holds.
- 6030.2  INDs: Review of Informed Consent Documents (Issued 11/13/2002)
- 6030.4 INDs: Screening INDs.  (Issued 5/9/2001, Posted 5/14/2001). This MaPP describes procedures for the review of multiple active moieties or formulations under the single investigative new drug application (IND) called a screening IND.


- 6030.8  INDs: Exception from Informed Consent Requirements for Emergency Research. (Issued 2/4/2003)

IND Forms and Instructions

Forms for use in submitting INDs include:

- FDA 1571  Investigational New Drug Application
- FDA 1572  Statement of Investigator
- Instructions for completing FDA forms 1571 and 1572
- FDA Form Distributions Page  includes links to:
 Certification: Financial Interest and Arrangements of Clinical Investigators
 Disclosure: Financial Interest and Arrangements of Clinical Investigators
 MedWatch: FDA Medical Product Reporting Program—Voluntary
 MedWatch: FDA Medical Products Reporting Program—Mandatory
- For electronic form submissions, see ERSR

Emergency use of an Investigational Drug or Biologic

- FDA proposes rules overhaul to expand the availability of experimental drugs. The Agency also clarifies permissible charges to patients. FDA News (12/11/2006)
- The Guidance for Institutional Review Boards and Clinical Investigators contains information on: Obtaining an Emergency IND, Emergency Exemption from Prospective IRB, Approval Exception from Informed Consent, and Requirement Planned Emergency Research, Informed Consent Exception.
- For assistance in obtaining unapproved cancer drugs, please see Access to Unapproved Drugs.
- Federal Register notice for Emergency Use of an Investigational New Drug; Technical Amendment 
- Directions to Sponsors of Emergency Investigational New Drug (EIND) Application. From the Office of Antimicrobial Products, Division of Antiviral Products (11/29/2005)

Emergency use requests:

- For investigational biological products regulated by CBER, call 301-827-2000.
- For all other investigational drugs, call 301-827-4570.
- After working hours, call FDA's Office of Emergency Operations at 301-443-1240.

Related Topics

- New Drug Application (NDA) Web page provides resources to assist drug sponsors with submitting applications for approval to market a new drug.
- Abbreviated New Drug Application (ANDA) Web page provides resources to assist drug sponsors with submitting applications to market a generic drug.
- Biological Therapeutic Products Web page
- Drug Application Regulatory Compliance the approval process for new drug applications includes a review of the manufacturer's compliance with Current Good Manufacturing Practice. This Web page provides resources to help meet compliance.
- Small Business Assistance Program Web page
- Electronic Regulatory Submission and Review (ERSR) Web page provides information on electronic drug applications, application reviews, Electronic Document Room, and other ERSR projects.
- Post Drug-approval Activities The goal of CDER's post drug-approval activities is to monitor the ongoing safety of marketed drugs. This is accomplished by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk.

FDA/Center for Drug Evaluation and Research

Last Updated: May 3, 2007

Originator: OTCOM/DML

HTML by SJW

Appendix B

Children's Healthcare of Atlanta	Document Control	
Standard Operating Procedure	Doc. No.: REG 001	Rev. No.: 0
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INFORMED CONSENT SUBMISSION, REVISION AND APPROVAL GUIDANCE

I. Purpose

To outline activities and procedures for modifying informed consent templates sent from the Sponsor per reviewing Institutional Review Board (IRB) requirements in preparation for submission to the IRB.

II. Scope

Applies to all personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Coinvestigator(s) and, *when delegated by the investigator*, subinvestigator(s) and clinical research coordinators. Hospital Medical Staff Office policies on credentialing may define personnel allowed to perform informed consent activities.

III. Background

Informed consent templates are either written by the principal investigator for his/her study or are sent from the Sponsor to the site. This document must contain the required language per the IRB policies and procedures. The revised informed consent submitted to the IRB must be approved by the Sponsor prior to submission.

In accordance with:

Title 21 CFR 50.20—General Requirements for Informed Consent

Title 21 CFR 50.25—Elements of Informed Consent

ICH GCP Consolidated Guideline—Part 4.8 Informed Consent of Trial Subjects

The Declaration of Helsinki (June 1964)

The Belmont Report (1979)

Office for Human Research Protections guidance document located at (<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm>)

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IV. Procedure

1. The Principal Investigator will obtain the informed consent template from the Sponsor for the protocol. The consent will be modified to include IRB required language and site required language by the person in charge of regulatory affairs.
2. The Principal Investigator may delegate the development and processing of the consent form to appropriate clinical sites research or regulatory personnel.
3. The Principal Investigator or his/her designee will make certain the cost/compensation language in the consent and the negotiated study budget concerning payments for research related expenses, patient stipends, etc., agree.
4. A footer will be inserted at the bottom of the page of the informed consent document designating version number and date.
5. The regulatory affairs person will send the revised consent (with tracked or highlighted changes) to the Sponsor for approval prior to submission to the IRB. This can be done by fax or e-mail.
6. Once approved, a copy of the Sponsor's approval (e-mail, fax or note to file re telephone approval) of the consent document will be kept in the correspondence section of the regulatory notebook or files.
7. Once approval for the revised document is obtained, the regulatory coordinator will accept all changes in the document.
8. The Sponsor approved consent will be submitted to the IRB for review and approval with the protocol and other required materials.
9. The Principal Investigator will revise the written consent form and any other written information to be provided to subjects whenever important new information becomes available that may be relevant to the subjects' continued participation. The Principal Investigator may delegate the development and processing of the revised consent form or any other written information to be provided to subjects to appropriate clinical site research personnel. Any such revisions must receive Sponsor and IRB approval prior to use.

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10. If the written consent form is revised during the course of a trial due to an amendment, change in the cost/compensation section, or addition of risk information based on adverse events, Data Safety Monitoring Boards (DSMB) or safety reports, the revisions will be added to the informed consent and approved by the Sponsor prior to submission to the IRB in the same manner described above.

Appendix C Children's Healthcare of Atlanta Consent to be in a Research Study

Title:

Principal Investigator:

Sponsor's Name: *If the study is not funded, delete this section*

If this form is being read by the parent or legal guardian, the term "you" refers to "your child."

You are being asked to volunteer for participation in a research study. In order to decide whether or not you want to be a part of this study, it is important that you read and understand this form. It is also important that you ask any questions that you may have and that you understand all the information in this form. This process is called "informed consent."

Why is this study being done?

Guidelines:

- *Describe the purpose(s) and give a description of the research*
- *An explanation of why the subject is being ask to volunteer*
- *Give number of anticipated subjects at Children's and nationwide, if applicable*

What will happen to you in this study?

Guidelines:

- *Provide a detailed, chronological description of all procedures to be performed.*
- *If the study involves random assignment, explain randomization in lay terms (for example, "like flipping a coin").*
- *Experimental procedures must be stressed and very clearly distinguished from the non-experimental procedures (routine care).*
- *If blood is drawn, indicate the amount in lay terms (teaspoons). Distinguish between blood drawn at each visit and the total amount of blood to be drawn for the entire study.*
- *If placebo is involved, explain this in lay terms.*
- *Provide a full explanation of all responsibilities and expectations of the subject.*
- *If the protocol includes a biological component which requires that specimens are sent to other researchers include the following:*
 1. *State whether the samples are strictly for research purposes and what will happen to the sample after the research is completed.*
 2. *If the samples are to be banked for future research, provide check boxes for the subject to agree to or not to agree to future unknown research.*
 3. *State whether the subject can opt-out at a later date (dependent on whether samples are identified or not) and how the subject may accomplish that.*
 4. *State whether or not results from this research will be available to the subject or not.*

How long will you be in this study?

Guidelines:

- *Indicate how much of the subject's time will be involved at each visit.*
- *State how long the subject's participation in the study will last.*

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 30, 2005 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

What are the possible risks to being in this study?

Guidelines:

- *Inform the subject of all foreseeable risks or discomforts for all study procedures. Those described should include any foreseeable physical, social, economic and psychological risks. Additionally, include the following sentence to address unforeseeable risks: Due to the investigational nature of this study there may be risks, discomforts or side effects that are not yet known.*
- *If blood is drawn state the following: There may be slight pain when the arm is stuck with the needle. A bruise may be left at the spot where the arm is stuck. There is a slight chance of swelling of the vein and/or blood clots, but this is extremely rare.*
- *Any risks to the subject or to a fetus if a female subject becomes pregnant while participating in the study must be stated. Risks or side effects that are known or may be currently unforeseeable should be described and steps which should be taken by the patient to avoid such risks. State what steps are required to insure that subject is not pregnant, what steps the subject should take to avoid pregnancy, and what the subject should take if she discovers she is pregnant.*

What are the possible benefits of being in this study?

Guidelines:

- *Do not refer to financial compensation or free drugs/treatment in this section.*
- *Any benefits to the subject or other's which may be reasonably expected should be described in a way that is not coercive, enticing or self-serving.*
- *That there may be no direct benefit to the subject. In this case, include the following: Taking part in this research study will not benefit you personally but we may learn new things that may help others in the future.*

What are the alternatives to being in this study?

Guidelines:

Describe all procedures or courses of treatment available to the subject outside of this study that might be advantageous to him/her.

The following is acceptable wording for this section if there are no other alternative treatments or procedures:

If the study does not involve treatment, state that "The alternative is to not participate, as this study does not involve treatment."

or

If you choose not to participate in this study your treatment will not be affected.

What is the cost of being in this study?

Guidelines:

- *If the subject is likely to incur any costs, this must be stated.*
- *Explain who the costs will be paid by or if there is no cost to the subject for participating.*
- *State whether the subject will be paid for participating in the study. If subjects are to be paid the anticipated amount of payment should be stated.*

What if you are injured while in this study?

Delete this section if the research does not pose more than minimal risk to the subject.

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 30, 2005 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

We will arrange for emergency care or medical treatment if you are injured by this research. Neither you nor your parent(s)/guardian(s) will be reimbursed for medical care other than what your insurance carrier may provide, nor will you or your parent(s)/guardian(s) receive other compensation. Children's Healthcare of Atlanta, Inc. and its affiliated corporations [*add any other study sites involved, such as name of private practice*] have not set aside funds to pay for this care or to compensate you if an injury occurs. For more information about risks or if you believe you have been injured by this research, you should contact [*insert Principal Investigator*] at [*insert phone number – ensure it directly connects to the PI, or else provide directions for reaching the PI, especially if it connects to a phone tree, administrative assistant, or message service and if this changes after regular office hours*].

Some sponsors do pay for medical care when injury occurs. Such provisions should be described in a separate paragraph.

What if there is new information about this study?

Include this section only if subjects will be informed of significant new information found during the course of the study or of changes to the study plan that might affect their decision to participate. This would be applicable, for instance, to a long-term treatment study and not applicable, for instance, to a one-time survey study.

We may learn new things during the study that you may need to know. We may also learn about things that might make you want to stop participating in the study. We will tell you about any new information.

What if you have any questions or problems while in this study?

If you have any questions about this study call [*insert Principal Investigator or other study consent person's name*] at [*insert phone number – ensure it directly connects to the PI, or else provide directions for reaching the PI, especially if it connects to a phone tree, administrative assistant, or message service and if this changes after regular office hours*]. If you have any questions about your rights as a participant in this study, you can call the Children's Healthcare of Atlanta Institutional Review Board (IRB) at (404) 785-7477. The IRB is a committee of people that approves all research in this hospital and follows all the rules and regulations made by government agencies about how research is done.

Who will be able to see your records of study participation?

If you are collecting PHI you must complete a stand alone "Authorization to Release Protected Health Information for Research Purposes". If you are not recording any PHI, describe exactly what information will otherwise be used and how you are going to maintain confidentiality.

Your records of participation in this study are not accessible to the general public and every effort will be made to maintain confidentiality. However, all records may be subject to subpoena by a court of law. Information that may be gained from this study will be used only for research and educational purposes. Information may be published in medical journals with permission of the Principal Investigator, [*insert name*], but your identity will not be revealed or written in a way that you can be recognized. Additionally, identifying information will be available to people from the Children's Healthcare of Atlanta IRB [*as applicable, also list collaborating institution's IRBs*].

What are your rights as a study participant?

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 30, 2005 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

Taking part in this study is completely voluntary. You may choose not to take part in this study. If you take part in this study, you may stop being in the study at any time. Your decision to not take part in the study or to stop being in the study will not in any way affect your current or future medical care at this hospital.

The study doctor may stop you from taking part in this study for any of the following reasons: (1) it would be dangerous for you to continue; (2) you do not follow study procedures; or (3) the study sponsor decides to end the study. [*Only list (1) and (2) if the study is not funded*]

Your signature below indicates that you have read this informed consent form and understand its meaning, you have been given the chance to ask questions and have had those questions answered to your satisfaction, and you voluntarily agree to participate in this study and sign this informed consent form. You will be given a copy of the signed informed consent form.

Printed Name of Research Subject

Age

Date of Birth

Signature of Research Subject

Date

Time

(Required unless research subject is under the age of 18 years and assent was not obtained for reason provided below)

Signature of Research Subject's Parent/Legal Guardian

Date

Time

(Required for research subjects under the age of 18 years)

Signature of Research Subject's Parent/Legal Guardian

Date

Time

(Required for research subjects under the age of 18 years when study poses more than minimal risk to the subject without the prospect of direct benefit)

Signature of Person Obtaining Assent/Consent/Permission

Date

Time

Signature of Witness

Date

Time

Signature of Interpreter

Date

Time

CHOA IRB#:
Children's IRB Approval Date:
Children's IRB Expiration Date:

Template version date: March 30, 2005 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

"In my opinion, the child is too young to assent to participate in this research study."

Signature of Person Obtaining Assent/Consent/Permission Date Time

CHOA IRB#:
Children's IRB Approval Date:
Children's IRB Expiration Date:

Template version date: March 30, 2005 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

Appendix D

U.S. Department of Health and Human Services National Institutes of Health HIPAA Privacy Rule Information for Researchers

Clinical Research and the HIPAA Privacy Rule

Researchers who conduct interventional clinical research have questioned how the Privacy Rule will affect their research activities. Even before the Privacy Rule, of course, physician-investigators have been concerned about the privacy of the medical and research-related information of their patients and subjects. In fact, many have been required under the Department of Health and Human Services (HHS) or the Food and Drug Administration (FDA) Protection of Human Subjects Regulations (45 CFR part 46 or 21 CFR parts 50 and 56, respectively) to take measures to protect such personal health information from inappropriate use or disclosure.

Moreover, in clinical research, physician-investigators often stand in dual roles to the subject: As a treating physician and as a researcher. For the treating physician, duties of confidentiality have long been established under well-known legal and ethical standards. The Privacy Rule adds to these existing obligations. Where a covered entity conducts clinical research involving protected health information (PHI), physician-investigators need to understand the Privacy Rule's restrictions on the use and disclosure of PHI for research purposes. As the federal privacy standards are implemented throughout the country, one benefit is that many clinical researchers and hospitals may adhere to a common set of national standards for protecting the privacy of patients and clinical research subjects.

This fact sheet discusses the Privacy Rule and its impact on covered entities that conduct clinical research. It places specific emphasis on the Authorization that is generally required for research uses and disclosures of PHI by covered entities. Additional information about the Privacy Rule's potential impact on other research activities, such as repositories, databases, health services research, Institutional Review Boards (IRBs), and Privacy Boards can be found in related publications, including:

- *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*
- *Health Services Research and the HIPAA Privacy Rule*
- *Research Repositories, Databases and the HIPAA Privacy Rule*
- *Institutional Review Boards and the HIPAA Privacy Rule*
- *Privacy Boards and the HIPAA Privacy Rule*

Introduction to the Privacy Rule

In response to a congressional mandate in the Health Insurance Portability and Accountability Act (HIPAA) of 1996, HHS issued regulations entitled *Standards for*

Privacy of Individually Identifiable Health Information. For most covered entities, compliance with these regulations, known as the Privacy Rule, was required as of April 14, 2003.

The Privacy Rule is a response to public concern over potential abuses of the privacy of health information. The Privacy Rule establishes a category of health information, referred to as PHI, which may be used or disclosed to others only in certain circumstances or under certain conditions. PHI is a subset of what is termed *individually identifiable health information*. With certain exceptions, the Privacy Rule applies to individually identifiable health information created or maintained by a covered entity. Covered entities are health plans, health care clearinghouses, and healthcare providers that transmit health information electronically in connection with certain defined HIPAA transactions, such as claims or eligibility inquiries. Researchers are not themselves covered entities, unless they are also healthcare providers and engage in any of the covered electronic transactions. If, however, researchers are employees or other workforce members of a covered entity (e.g., a hospital or health insurer), they may have to comply with that entity's HIPAA privacy policies and procedures. Researchers who are not themselves covered entities, or who are not workforce members of covered entities, may be indirectly affected by the Privacy Rule if covered entities supply their data. In addition, it should be noted that the HHS and FDA's Protection of Human Subjects Regulations (45 CFR part 46 and 21 CFR parts 50 and 56, respectively) may also apply to clinical research.

Overview of the Privacy Rule's Impact on Clinical Research

PHI includes what physicians and other health care professionals typically regard as a patient's personal health information, such as information in a patient's medical chart or a patient's test results, as well as an individual's billing information for medical services rendered, when that information is held or transmitted by a covered entity. PHI also includes identifiable health information about subjects of clinical research gathered by a researcher who is a covered health care provider.

The Privacy Rule permits a covered entity to use or disclose PHI for research under the following circumstances and conditions:

- If the subject of the PHI has granted specific written permission through an Authorization that satisfies section 164.508
- For reviews preparatory to research with representations obtained from the researcher that satisfy section 164.512(i)(1)(ii) of the Privacy Rule
- For research solely on decedents' information with certain representations and, if requested, documentation obtained from the researcher that satisfies section 164.512(i)(1)(iii) of the Privacy Rule

- If the covered entity receives appropriate documentation that an IRB or a Privacy Board has granted a waiver of the Authorization requirement that satisfies section 164.512(i)
- If the covered entity obtains documentation of an IRB or Privacy Board's alteration of the Authorization requirement as well as the altered Authorization from the individual
- If the PHI has been de-identified in accordance with the standards set by the Privacy Rule at section 164.514(a)-(c) (in which case, the health information is no longer PHI)
- If the information is released in the form of a limited data set, with certain identifiers removed and with a data use agreement between the researcher and the covered entity, as specified under section 164.514(e)
- Under a "grandfathered" informed consent of the individual to participate in the research, an IRB waiver of such informed consent, or Authorization or other express legal permission to use or disclose the information for research as specified under the transition provisions of the Privacy Rule at section 164.532(c)

Note that the Privacy Rule also permits covered entities to use and disclose PHI for purposes of treatment, payment, and health care operations without Authorization. The Privacy Rule also permits disclosures to business associates. Business associates are persons or entities that perform certain functions or services on behalf of the covered entity that require the use or disclosure of PHI, provided certain arrangements to safeguard the PHI are in place between the covered entity and the business associates. The Privacy Rule also permits, without Authorization, covered entities to make a number of other disclosures of PHI, including disclosures that are required by law, disclosures to public health authorities authorized by law to collect or receive such information for public health activities, and disclosures for adverse event reporting to certain persons subject to the jurisdiction of the FDA (e.g., clinical trial drug sponsors). (See section 164.512 for a description of other disclosures for which Authorization is not required.)

For a more detailed discussion of permitted uses or disclosures of PHI for research under the Privacy Rule, refer to *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule; Research Repositories, Databases, and the HIPAA Privacy Rule; Institutional Review Boards and the HIPAA Privacy Rule; and Privacy Boards and the HIPAA Privacy Rule*.

Authorization for PHI Uses and Disclosures

A valid Privacy Rule Authorization is an individual's signed permission that allows a covered entity to use or disclose the individual's PHI for the purpose(s) and to the recipient(s) stated in the Authorization. When an Authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to

future, unspecified projects. If an Authorization for research is obtained, a covered entity's uses and disclosures must be consistent with what is stated in the Authorization.

An Authorization differs from an informed consent in that an Authorization is an individual's permission for a covered entity to use or disclose PHI for a certain purpose, such as a research study. An informed consent, on the other hand, is the individual's permission to participate in the research. An informed consent provides research subjects with a description of the study and of its anticipated risks and/or benefits, and a description of how the confidentiality of records will be protected, among other things. An Authorization can be combined with an informed consent document or other permission to participate in research. Whether combined with an informed consent or separate, an Authorization must contain the specific core elements and required statements stipulated in the Privacy Rule. A related publication, *Sample Authorization Language*, demonstrates the inclusion of core elements and required statements for Authorizations.

Authorization Core Elements

- A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner
- The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure
- The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure
- A description of each purpose of the requested use or disclosure
- Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository)
- Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided

Authorization Required Statements

- A statement of the individual's right to revoke Authorization and how to do so, and, if applicable, the exceptions to the right to revoke Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
- Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
- A statement of the potential risk that PHI will be re-disclosed by the recipient and no longer protected by the Privacy Rule. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

Limits on Using and Disclosing PHI if Authorization is Revoked

Although an Authorization for research uses and disclosures need not expire, a research subject has the right to revoke, in writing, Authorization at any time. The individual's revocation is effective when the covered entity receives the written revocation, except to the extent that the covered entity has taken action in reliance upon the Authorization. For example, a covered entity is not required to retrieve information that it disclosed under a valid Authorization before receiving the revocation. For research uses and disclosures, the reliance exception would permit the continued use and disclosure of PHI already obtained pursuant to the Authorization to the extent necessary to protect the integrity of the research—for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events.

Activities Preparatory to Research

Covered entities may permit researchers to review PHI in medical records or elsewhere during reviews preparatory to research. These reviews allow the researcher to determine, for example, whether there is a sufficient number or type of records to conduct the research. Importantly, the covered entity may not permit the researcher to remove any PHI from the covered entity. To permit the researcher to conduct a review preparatory to research, the covered entity must receive from the researcher representations that:

- The use or disclosure is sought solely to review PHI as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the covered entity during the review.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Additional information on activities preparatory to research can be found in the booklet, *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*.

Identifying Research Participants

Under the "preparatory to research" provision, covered entities may use or disclose PHI to researchers to aid in study recruitment. The covered entity may allow a researcher, either within or outside the covered entity, to identify, but not contact, potential study participants under the "preparatory to research" provision. However, before permitting this activity, a covered entity must receive proper representation, as described above, from the researcher. Under the "preparatory to research" provision, no PHI may leave the covered entity.

Contacting Research Participants

Under the "preparatory to research" provision, covered entities may use and disclose PHI to researchers to aid in study recruitment. They may allow a researcher to identify, but

not contact, potential study participants. To contact potential study participants, a researcher may do so, without Authorization from the individual, under the following circumstances:

- If the researcher is a workforce member of a covered entity, the researcher may contact the potential study participant, as part of the covered entity's health care operations, for the purposes of seeking Authorization. In addition, a covered health care provider may discuss treatment alternatives, which may include participating in a clinical trial, with the patient as part of the patient's treatment or the covered entity's health care operations. Alternatively, the covered entity may contract with a business associate—who may be a researcher—to assist in contacting individuals on behalf of the covered entity to obtain their Authorizations.
- If the covered entity obtains documentation that an IRB has partially waived the Authorization requirement to disclose PHI to a researcher for recruitment purposes, the covered entity could disclose to the researcher that PHI necessary for the researcher to contact the individual.

Research Uses and Disclosures Under Permissions Obtained Prior to the Privacy Rule's Compliance Date

Sections 164.532(a) and (c) of the Privacy Rule provide that, after the compliance date (for most covered entities, April 14, 2003), a covered entity may use or disclose an individual's PHI without an Authorization, or waiver or alteration of the Authorization requirement, in connection with research, if specific conditions are met. For many such uses and disclosures of PHI in connection with research, a covered entity may rely on any one of the following that was obtained prior to the compliance date:

- An Authorization or other express legal permission from an individual to use or disclose PHI for research
- The informed consent of the individual to participate in the research
- A waiver by an IRB of informed consent in accordance with applicable laws and regulations governing informed consent, unless a new informed consent document is sought after the compliance date

The transition provisions do not apply if any change is made after the compliance date to an informed consent, express legal permission, or IRB waiver for the research obtained before the compliance date that would invalidate these prior permissions. In such cases, an Authorization that complies with section 164.508 of the Privacy Rule is required unless the activity is otherwise permitted by the Privacy Rule without Authorization (e.g., through a waiver of Authorization).

In some instances, express legal permissions, informed consents, or IRB-approved waivers of informed consents are not study specific. These permissions for research and waivers, if obtained before the compliance date, are grandfathered by the transition

provisions even if provided for future unspecified research, subject to the conditions described above.

Frequently Asked Questions and Answers

Q: What is the relationship between the Privacy Rule and the HHS and FDA Protection of Human Subjects Regulations?

A: There are two main differences. First, the HHS and FDA Protection of Human Subjects Regulations are concerned with the risks associated with participation in research. These may include, but are not limited to, the risks associated with investigational products and the risks of experimental procedures or procedures performed for research purposes, and the confidentiality risks associated with the research. The Privacy Rule is concerned with the risk to the subject's privacy associated with the use and disclosure of the subject's PHI.

Second, the scope of the HHS and FDA Protection of Human Subjects Regulations differs from that of the Privacy Rule. The FDA regulations apply only to research over which the FDA has jurisdiction, primarily research involving investigational products. The HHS Protection of Human Subjects Regulations apply only to research that is conducted or supported by HHS, or conducted under an applicable Office for Human Research Protections (OHRP)-approved assurance where a research institution, through their Multiple Project Assurance (MPA) or Federal-Wide Assurance (FWA), has agreed voluntarily to follow the HHS Protection of Human Subjects Regulations for all human subjects research conducted by that institution regardless of the source of support. By contrast, the Privacy Rule applies to a covered entity's use or disclosure of PHI, including for any research purposes, regardless of funding or whether the research is regulated by the FDA.

Q: Under certain circumstances, the "preparatory to research" provision at section 164.512(i)(1)(ii) of the Privacy Rule permits covered entities to use or disclose PHI for purposes preparatory to research. What kinds of activities are considered "preparatory to research"?

A: Covered entities that obtain certain required representations from a researcher may use and disclose PHI for activities "preparatory to research" that include, but are not limited to, the following:

- Preparing a research protocol
- Assisting in the development of a research hypothesis
- Aiding in research recruitment, such as identifying prospective research participants who would meet the eligibility criteria for enrollment into a research study

Under this provision, no PHI may be removed from the covered entity during the course of the review.

Q: When do the requirements under HHS regulations at 45 CFR part 46 related to IRB review and informed consent apply to "preparatory to research" activities as permitted by the Privacy Rule at section 164.512(i)(1)(ii)?

A: HHS Protection of Human Subjects Regulations at 45 CFR part 46 do not reference "preparatory to research" activities.

HHS regulations at 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."

HHS regulations at 45 CFR 46.102(f) define "human subject" as

a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information... *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

When a "preparatory to research" activity (i) involves human subjects research, as defined above; (ii) is conducted or supported by HHS or conducted under an applicable OHRP-approved assurance; and (iii) does not meet the criteria for exemption under HHS regulations at 45 CFR 46.101(b), the research must be reviewed and approved by an IRB in accordance with HHS regulations at 45 CFR 46.109(a). In addition, informed consent of the subjects must be sought and documented in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117, respectively. However, under HHS Protection of Human Subjects Regulations at 45 CFR 46.116(c) and (d), an IRB may approve a consent procedure for such a "preparatory to research" activity that does not include, or that alters, some or all of the elements of informed consent, or may waive the requirements to obtain informed consent for such a "preparatory to research" activity if certain criteria are satisfied.

The Privacy Rule permits, under section 164.512(i)(1)(ii), a covered entity to provide investigators with access to PHI for purposes preparatory to research, such as for purposes of identifying potential human subjects to aid in study recruitment, among other things. Such access is permitted provided that the covered entity receives certain required representations from the researcher and the researcher does not remove any PHI from the covered entity during the course of the review.

Activities in which an investigator obtains and records individually identifiable health information for purposes of identifying potential human subjects to aid in study

recruitment, among other things, would involve human subjects research under the HHS regulations at 45 CFR part 46 and would not satisfy the criteria for any exemption under HHS regulations at 45 CFR 46.101(b). As a result, if such activities are conducted or supported by HHS or conducted under an applicable OHRP-approved assurance, the research activities must be reviewed and approved by an IRB in accordance with HHS regulations at 45 CFR 46.109(a). In addition, informed consent of the subjects, about whom identifiable private information (e.g., health information) is being obtained, must be sought and documented in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117, respectively.

For example, if an investigator who is covered by an applicable OHRP-approved assurance obtains and records identifiable private information from medical records for the purpose of contacting these individuals to determine if they would be interested in participating in a research study, this activity constitutes human subjects research and thus would require either (1) that subjects' informed consent be sought as required by the HHS regulations at 45 CFR 46.116 or (2) that the IRB approve an informed consent procedure that does not include or that alters some or all of the elements of informed consent, or waive the requirement to obtain informed consent in accordance with the provisions of the HHS regulations at 45 CFR 46.116(c) or (d). Informed consent also must be documented in accordance with, and to the extent required by, the HHS regulations at 45 CFR 46.117.

Similarly, if such an investigator obtains and records identifiable private information to develop a database of potential research subjects for future research studies, this activity is also human subjects research as defined in 45 CFR part 46 and thus must meet the requirements of the HHS regulations as discussed above.

The above interpretation does not conflict in any way with OCR's interpretation of the Privacy Rule. It should be noted that Authorization for use or disclosure of PHI provided for under the Privacy Rule and legally effective informed consent for research provided for under HHS regulations at 45 CFR 46.116 and 46.117 are not the same.

Furthermore, the Privacy Rule does not override any requirements of 45 CFR part 46, and vice versa. In situations where both 45 CFR part 46 and the Privacy Rule apply, institutions must adhere to both sets of regulations.

Q: If, under the "preparatory to research" provisions, a researcher identifies subjects that meet the study's eligibility criteria, how can the researcher contact the potential participant to obtain Authorization after identifying these individuals?

A: Under the "preparatory to research" provision, covered entities may use and disclose to researchers PHI to aid in study recruitment. They may allow a researcher to identify, but not contact, potential study participants. In order to contact potential study participants, a researcher may do so, without Authorization from the individual, under the following circumstances:

- If the researcher is a workforce member of a covered entity, the researcher may contact the potential study participant, as part of the covered entity's health care operations, for the purposes of seeking Authorization. Alternatively, the covered entity may contract with a researcher as a business associate to assist in contacting individuals on behalf of the covered entity to obtain their Authorizations.
- If the covered entity obtains documentation that an IRB has partially waived the Authorization requirement to disclose PHI to a researcher for recruitment purposes, the covered entity could disclose to the researcher that PHI necessary for the researcher to contact the individual.

Q: Is a covered entity required to account for disclosures made pursuant to an IRB or Privacy Board's alteration of the Authorization requirement?

A: Yes. Covered entities are required to account for disclosures made pursuant to an altered Authorization. Where an Authorization has been altered, pursuant to the process provided for by section 164.512(i) of the Privacy Rule, it is no longer an "authorization as provided in section 164.508" and thus, no longer exempt from the accounting requirements pursuant to section 164.528(a)(1)(iv). However, where a covered entity discloses the records of 50 or more individuals for a particular research purpose during the period covered by the accounting, the Privacy Rule permits the covered entity to provide a more general accounting to the requestor. See section 164.528(b)(4) of the Privacy Rule. The period covered by the accounting is no more than 6 years prior to the date on which the accounting is requested (or less than 6 years if requested by the individual) but does not include disclosures made prior to the compliance date-usually April 14, 2003.

Q: When must an IRB review and approve the language of an Authorization for use or disclosure of PHI related to human subjects research activities regulated by HHS Protection of Human Subjects Regulations at 45 CFR part 46 and FDA Protection of Human Subjects Regulations at 21 CFR parts 50 and 56?

A: The HHS and FDA Protection of Human Subjects Regulations do not expressly require that Privacy Rule Authorizations be reviewed or approved by an IRB. However, under HHS regulations at 45 CFR 46.117(a) and FDA regulations at 21 CFR 50.27(a), IRB review and approval is required for any document that contains the required informed consent document for human subjects research. Therefore, if the Authorization language is part of the informed consent document, such as when the Authorization form is combined with an informed consent form, the IRB is required to review such language.

Generally, neither HHS regulations at 45 CFR part 46 nor FDA regulations at 21 CFR parts 50 and 56 require that stand-alone Authorizations (i.e., Authorizations that are not incorporated into the informed consent document) for use or disclosure of PHI be reviewed and approved by the IRB. However, FDA regulations at 21 CFR 56.108(a) would require such review if required by the IRB's written procedures. In the exercise of ongoing enforcement discretion, however, with respect to the requirements of 21 CFR 56.108(a), to the extent that an IRB's written procedures require the review and/or

approval of stand-alone Authorizations, FDA will not take enforcement action against an IRB for failing to review them even when the IRB's written procedures otherwise would require such review and/or approval.

The Privacy Rule does not require IRBs to review or approve Authorizations used for research or other disclosures; it only requires that the Authorization comply with the requirements of the Rule at section 164.508. For Office for Civil Rights (OCR) guidance on this topic, see <http://www.hhs.gov/ocr/hipaa/privguideresearch.pdf>.

Q: Does the Privacy Rule require IRBs to review and/or approve Authorizations, either as stand-alone documents (i.e., Authorizations that are not combined with informed consent documents) or when combined with informed consent?

A: No.

Q: Do FDA regulations require IRBs to review and/or approve stand-alone Authorizations, i.e., Authorizations that are not combined with informed consent documents?

A: No. FDA regulations do not specifically require IRBs to review and/or approve stand-alone Authorizations. However, FDA regulations governing IRBs require, in pertinent part, that IRBs adopt and follow written procedures for reviewing clinical research. See 21 CFR 56.108(a). Pursuant to this provision, IRBs that have written procedures requiring them to review all written materials provided to potential research subjects would have to review and approve stand-alone Authorizations, even though such review is not otherwise required under the Privacy Rule, HHS Protection of Human Subjects Regulations, or FDA regulations governing IRBs. However, in the exercise of ongoing enforcement discretion with respect to the requirements of 21 CFR 56.108(a), to the extent that an IRB's written procedures require the review and/or approval of stand-alone Authorizations, FDA will not take enforcement action against an IRB for failing to review them even when the IRB's written procedures otherwise would require such review and/or approval. For OCR guidance on this topic, see <http://www.hhs.gov/ocr/hipaa/privguideresearch.pdf>.

Q: Do international guidelines (the ICH Good Clinical Practice Guidelines) require IRBs to review and/or approve stand-alone Authorizations, i.e., Authorizations that are not combined with informed consent documents?

A: No. The International Conference on Harmonisation (ICH) Good Clinical Practice: Consolidated Guideline (E6) states, for example, "Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC [Independent Ethics Committee] for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), *and any other written information to be provided to subjects.*" (Emphasis added.) (See ICH E6 4.4.1.) This language recommends, but does not require,

such review. In general, the ICH Good Clinical Practice guidelines are recommendations, not legal requirements. As such, they are not subject to enforcement by U.S. authorities.

Q: May a covered health care provider discuss with a patient his or her enrollment in clinical research without the patient's Authorization? What if the individual is not a patient of the covered provider?

A: Yes. These types of conversations may arise under a variety of circumstances. For example, a physician may for treatment purposes discuss treatment alternatives with the individual, which may include the option of enrolling in a clinical trial. In addition, a physician may speak to the individual about a clinical trial as part of asking the individual to sign an Authorization to permit the covered provider to use or disclose the individual's PHI for the research study. Also, the Privacy Rule generally permits a covered entity to communicate with individuals and to disclose their PHI to them. Therefore, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient Authorization, regardless of whether the individual is a patient of the covered provider, and without an IRB or Privacy Board waiver of the Authorization. However, the covered health care provider must obtain the individual's Authorization or an IRB or Privacy Board waiver of Authorization, or meet certain other conditions, before using or disclosing the individual's PHI as part of the research study.

Similarly, if a physician knows of a study in which his or her patient might enroll that is being conducted by others, the physician may discuss such a trial with the patient and give the patient the researcher's contact information so the patient may contact the researcher directly. However, the physician may only contact the researchers about the patient so long as de-identified information is disclosed, the individual's Authorization or IRB or Privacy Board waiver of Authorization is obtained, or other conditions that satisfy the Privacy Rule are met. For example, it is acceptable to give a clinical summary of a patient to a researcher to determine if the patient might meet enrollment criteria, if such discussions omit the patient's name, address, medical record number, and any other identifying information set forth in section 164.514(a)-(c) of the Privacy Rule.

Q: May a covered entity obtain an individual's Authorization to include his or her PHI in a clinical research recruitment database of possible research participants, such as a pre-screening log?

A: Yes. The Privacy Rule permits a covered entity to include an individual's PHI in a clinical research recruitment database and permit researchers access to the recruitment database, provided the individual has given permission through a written Authorization. The Authorization must inform the individual of the purpose for which (e.g., for the pre-screening log for one or more clinical trials) and what PHI will be used and meet the other requirements at section 164.508 of the Privacy Rule. Alternatively, a covered entity may provide a researcher access to the PHI for reviews preparatory to research, provided the required representations are obtained. See section 164.512(i) of the Privacy Rule. Unless otherwise permitted by the Privacy Rule, a subsequent Authorization must be

obtained from the individual before a covered entity may use or disclose the individual's PHI for the clinical trial itself.

Q: One common method for recruiting research participants involves organizing a call center for potential research participants to contact in response to advertisements about the research. Would a call center be required to obtain the individual's Authorization before speaking to the individual about the trial?

A: Call centers in many cases will not be part of a covered entity (health plan, health care clearinghouse, certain health care providers), and thus, are not required to comply with the Privacy Rule. A call center for research is an entity established to receive and answer calls from interested individuals about a research project. Commonly, a call center will collect identifiable information about a caller who may be interested in the research study and then transmit such information to researchers involved in the study or send information about a study directly to callers.

If a call center is part of a covered entity, e.g., part of a covered health care provider that is also a researcher, it may speak with an individual without Authorization for purposes of communicating about the research study or obtaining the individual's Authorization to use or disclose his or her PHI for the study. However, any use or disclosure of the individual's PHI for the research study itself or other purposes is subject to the conditions set forth in the Privacy Rule.

Q: Is a covered health care provider that conducts clinical research required to provide the Notice of Privacy Practices to participants of that trial?

A: Maybe. The Privacy Rule requires covered health care providers that have a direct treatment relationship with the individuals to provide to individuals the Notice of Privacy Practices in accordance with section 164.520(c)(2). A direct treatment relationship means a treatment relationship between an individual and a health care provider that is not an indirect treatment relationship. An indirect treatment relationship between an individual and a health care provider is one in which:

- The health care provider delivers health care to the individual based on the orders of another health care provider.
- The health care provider typically provides services or products, or reports the diagnosis or results associated with the health care, directly to another health care provider, who provides the services or products to the individual.

Where a covered health care provider does not have a direct treatment relationship with the individual, the Privacy Rule does not require that provider to give to the individual the Notice of Privacy Practices. However, the covered provider is still responsible for making its Notice of Privacy Practices available to any person that requests it, and prominently posting and making available its Notice of Privacy Practices on any Web site it maintains that provides information about its customer services or benefits.

Q: How does the written Authorization required under the Privacy Rule differ from the written informed consent required under the HHS and FDA Protection of Human Subjects Regulations?

A: Under the Privacy Rule, a patient's Authorization is for the use and disclosure of PHI, which can include use or disclosure for research purposes. In contrast, an individual's informed consent, as required by the HHS or FDA Protection of Human Subjects Regulations, is a consent to participate in the research study as a whole, not simply a consent for the research use or disclosure of PHI. While there are important differences between the Privacy Rule's requirements for individual Authorization, and HHS' or FDA's Protection of Human Subjects Regulations requirements for informed consent, the Privacy Rule's Authorization elements are compatible with the informed consent elements of the HHS Protection of Human Subjects Regulations. Thus, both sets of requirements can be met by use of a single, combined form, which is permitted by the Privacy Rule. For example, the Privacy Rule allows the Authorization for research to state that the Authorization will be valid until the conclusion of the research study, or to state that the Authorization will not have an expiration date or event. This is compatible with HHS' Protection of Human Subjects Regulations requirement for an explanation of the expected duration of the research subject's participation in the study. It should be noted that where the Privacy Rule, the HHS Protection of Human Subjects Regulations, and/or FDA's Protection of Human Subjects Regulations apply, each applicable regulation must be followed.

Q: May the Authorization required under the Privacy Rule be part of the informed consent document required under the HHS and FDA Protection of Human Subjects Regulations?

A: Yes. The two documents may be combined, or they may be separate.

Q: If an Authorization to use or disclose PHI for research is combined with an informed consent form, does a covered entity need to obtain a signature authorizing the use or disclosure of PHI separately from a signature that may be required for informed consent under 45 CFR part 46 or 21 CFR parts 50 and 56?

A: No. Where an individual's signature is sought for a single form that combines Authorization with informed consent [also known as a compound Authorization at 164.508(b)(3)(i)], one signature satisfies the Authorization requirement at 164.508(c)(1)(vi).

Q: Do HHS regulations at 45 CFR part 46 and FDA regulations at 21 CFR parts 50 and 56 permit the IRB to review and approve the insertion of Authorization language as a single modification that applies to the informed consent documents of multiple protocols previously approved by the IRB?

A: Yes, when Authorizations for use or disclosure of PHI will be incorporated into previously approved informed consent documents for a series of protocols, and the

Authorizations are composed entirely of identical template language, the IRB may approve the insertion of the Authorization language as a single modification that applies to the entire series of protocols.

However, when Authorizations for use or disclosure of PHI will be incorporated into previously approved informed consent documents for a series of protocols and the Authorization statements include protocol-specific information unique to each of the protocols, the IRB should review and approve the insertion of the Authorization language separately for each protocol.

In both cases, an expedited review procedure may be used.

Q: Do the core elements of an Authorization differ from a medical records release form?

A: Probably. A Privacy Rule Authorization may be a more detailed document than what physicians and hospitals are accustomed to using as a release of medical records. Medical records release forms usually are phrased very generally, but Authorizations are much more specific with regard to what information is being released, to whom, for what purpose, and for how long. An Authorization must also inform patients of certain rights they have in relation to their PHI. An Authorization may contain more information than required by the Privacy Rule, as long as the additional information is not inconsistent with the information required for the Authorization. See section 164.508 for the specific requirements for a Privacy Rule Authorization.

Q: Does the Authorization form need to have a termination date for research?

A: No. An Authorization for research uses and disclosures need not have a fixed expiration date or state a specific expiration event; the form can list "none" or "the end of the research project."

Q: Must a separate Authorization be obtained for each research use or disclosure of PHI?

A: No. As long as each use or disclosure is part of a specific research activity and the Authorization describes the types of uses or disclosures that will occur as part of that research activity, only one Authorization is required from each subject. That Authorization will generally be obtained at the time of enrollment in the trial itself, as part of the informed consent process. It is important, therefore, that researchers, research nurses, or others involved in informed consent discussions with subjects also understand the Authorization and its meaning so that subjects' questions and concerns can be answered accurately.

Q: Does the Privacy Rule specify who must develop the Authorization form?

A: No. The Privacy Rule does not specify who may draft the Authorization, so a researcher could draft it. However, in order to comply with the Privacy Rule, an Authorization must be written in plain language and contain the core elements and required statements specified at section 164.508 of the Privacy Rule. A covered entity may disclose PHI as specified in a valid Authorization that has been created by another covered entity or a third party, such as a researcher.

Q: When a covered entity chooses to combine the Authorization with the informed consent document for a research study, can the compound document cross-reference required elements for both permissions (i.e., to minimize redundant language)?

A: Yes. The Privacy Rule permits the compound Authorization to cross-reference relevant sections of an informed consent document, provided the compound document includes the core elements and statements required by section 164.508(c). In addition, under the HHS and FDA Protection of Human Subjects Regulations, all of the required elements for informed consent must be included in the informed consent document, unless an IRB alters or waives the requirements.

Q: How may a covered entity use or disclose PHI for the creation of a research repository or database when it is unknown at the time of collection what specific protocols will make use of the repository or database in the future?

A: There are two separate activities to consider: (1) The use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research protocol.

A covered entity's use or disclosure of PHI to create a research database or repository, and use or disclosure of PHI from the database or repository for a future research purpose, are each considered a separate research activity under the Privacy Rule. In general, the Privacy Rule requires Authorization for each activity, unless, for example, an IRB or Privacy Board waives or alters the Authorization requirement. Documentation of a waiver or an alteration of Authorization to use or disclose PHI to create a research database requires, among other things, a statement that an IRB or Privacy Board has determined that the researcher has provided adequate written assurances that PHI in the database will not be further used or disclosed except as permitted by the Privacy Rule (e.g., for research uses and disclosures with an Authorization or waiver). A covered entity also could use or disclose a limited data set to create a research repository or database under conditions set forth in a data use agreement.

For subsequent use or disclosure of PHI for research purposes from a repository or database maintained by the covered entity, the covered entity may:

- Obtain the individual's Authorization for the research use or disclosure of PHI as specified under section 164.508

- Obtain documentation of an IRB or Privacy Board's waiver of the Authorization requirement that satisfies section 164.512(i)
- Obtain satisfactory documentation of an IRB or Privacy Board's alteration of the Authorization requirement as well as the altered Authorization from the individual
- Use or disclose PHI for reviews preparatory to research with representations that satisfy section 164.512(i)(1)(ii) of the Privacy Rule
- Use or disclose PHI for research on decedents' PHI with representations that satisfy section 164.512(i)(1)(iii) of the Privacy Rule
- Provide a limited data set and enter into a data use agreement with the recipient as specified under section 164.514(e)
- Use or disclose PHI based on permission obtained prior to the compliance date of the Privacy Rule— informed consent of the individual to participate in the research, an IRB waiver of such informed consent, or Authorization or other express legal permission to use or disclose the information for the research as specified under section 164.532(c) of the Privacy Rule

A covered entity may also use or disclose PHI from databases and repositories for other purposes without Authorization as permitted by the Privacy Rule, such as if required by law or to a public health authority for a public health activity (e.g., disclosures to public, including state, cancer registries). Covered entities may also de-identify PHI according to standards set forth in the Privacy Rule so that its use and disclosure is not protected by the Privacy Rule.

Q: What documentation of an IRB or Privacy Board waiver or alteration of the requirement for an Authorization must a covered entity receive in order to permit a use or disclosure of PHI for research without Authorization?

A: Under the Privacy Rule at section 164.512(i), a covered entity may use or disclose PHI for a research study without Authorization (or with an altered Authorization) from the research participant if the covered entity obtains proper documentation that an IRB or Privacy Board has granted a waiver (or alteration) of the Authorization requirements. Among other requirements under section 164.512(i), a covered entity must obtain a statement that an IRB or a Privacy Board has determined that the alteration or waiver, in whole or in part, of Authorization satisfies the following three criteria in the Privacy Rule:

1. The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
 - a. An adequate plan to protect the identifiers from improper use and disclosure.
 - b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research

justification for retaining the identifiers or such retention is otherwise required by law.

- c. Adequate written assurances that the PHI will not be reused or disclosed except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted by the Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI.

Clinical research will not generally qualify for a waiver of the Authorization if a clinical research participant will be asked to sign an informed consent before entering the study. We anticipate that waiver of Authorization will be more common in research that involves, for example, retrospective medical chart reviews. Additionally, when Authorization is waived for research access to medical records or other PHI, the covered entity must take reasonable steps to limit the information disclosed to that which is the minimum necessary for the research purpose. If appropriate documentation of an IRB or Privacy Board waiver or alteration of Authorization is presented to the covered entity, the covered entity may rely, if reliance is reasonable under the circumstances, upon documentation of such waiver that the request represents the minimum necessary amount of PHI for the research.

Q: Once an individual's information has been de-identified according to Privacy Rule standards, does the subject's Authorization have to be obtained for use or disclosure of that de-identified information for research?

A: No. De-identified information is not considered PHI and as such is not governed by the Privacy Rule, and no Authorization or waiver is necessary for its use or disclosure.

Q: Does a covered entity need an individual's Authorization before de-identifying the PHI or creating a limited data set?

A: No. The Privacy Rule does not require a covered entity to obtain an individual's Authorization before using or disclosing the PHI for creating de-identified health information or a limited data set. The Privacy Rule considers such activity to be a health care operation, as defined at section 164.501, of the covered entity. As such, a covered entity could contract with a business associate, including a researcher, to create de-identified data or a limited data set.

Q: What kind of information must be removed from health information in order for it to be de-identified?

A: The Privacy Rule provides two ways to de-identify PHI. One way is to remove the following identifiers of the individual and of the individual's relatives, employers, or household members: (1) Names; (2) all geographic subdivisions smaller than a state, except for the initial three digits of the zip code if the geographic unit formed by

combining all zip codes with the same three initial digits contains more than 20,000 people; (3) all elements of dates except year and all ages over 89; (4) telephone numbers; (5) fax numbers; (6) email addresses; (7) social security numbers; (8) medical record numbers; (9) health plan beneficiary numbers; (10) account numbers; (11) certificate or license numbers; (12) vehicle identifiers and license plate numbers; (13) device identifiers and serial numbers; (14) URLs; (15) IP addresses; (16) biometric identifiers; (17) full-face photographs and any comparable images; (18) any other unique, identifying characteristic or code, except as permitted for re-identification in the Privacy Rule.

In addition to removing these identifiers, the covered entity must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual.

Covered entities may also use statistical methods to establish de-identification instead of removing all 18 identifiers. The covered entity may obtain certification by "a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable" that there is a "very small" risk that the information could be used by the recipient to identify the individual who is the subject of the information, alone or in combination with other reasonably available information. The person certifying statistical de-identification must document the methods used as well as the result of the analysis that justifies the determination. A covered entity is required to keep such certification, in written or electronic format, for at least 6 years from the date of its creation or the date when it was last in effect, whichever is later.

Q: If a subject signed an informed consent to participate in clinical research prior to the Privacy Rule compliance date (April 14, 2003), does the researcher have to get the subject to sign an Authorization in order to use or disclose that subject's PHI after April 14, 2003?

A: No. Under the transition provisions of the Privacy Rule, as long as the informed consent was signed prior to April 14, 2003, the covered entity may use or disclose that subject's data, even if the data were not generated or received until after the compliance date, consistent with any agreed upon restriction on the use or disclosure of the information. However, the transition provision does not apply to the PHI of subjects enrolled after the compliance date (usually April 14, 2003). These subjects may have to complete an Authorization form, unless, for instance, an IRB or Privacy Board has approved a waiver of the Authorization requirement.

Q: If a use or disclosure could be made under the Privacy Rule as a research activity or another permitted activity, such as a permitted public health activity, does the use or disclosure have to satisfy both sets of requirements?

A: No. There may be cases where an activity may be permitted under more than one provision of the Privacy Rule, e.g., a disclosure for public health and research, such as for adverse event reporting. In this case, disclosures may be made under either the research

provisions or the public health provisions, as appropriate-the covered entity need not comply with both sets of requirements.

However, activities that are considered both public health and research under the Privacy Rule, and that also meet the definition of "research" as defined under the HHS Protection of Human Subjects Regulations, must be conducted in compliance with the HHS Protection of Human Subjects Regulations if the research is conducted or supported by HHS, or conducted under an applicable Assurance approved by the Office for Human Research Protections. Similarly, if an activity is both a public health and research activity that is subject to FDA's Protection of Human Subjects Regulations, then compliance with FDA's regulations would also be required.

Q: Would a covered entity be required to account for disclosures of PHI made pursuant to an informed consent or authorization for the research that was "grandfathered" under the transition provisions?

A: Yes, a covered entity would be required to account for such disclosures unless the consent or Authorization to participate in the research would constitute a valid Authorization under section 164.508 of the Privacy Rule.

Q: Does the Privacy Rule give subjects a right to access their research records during the course of a clinical trial?

A: The Privacy Rule does afford subjects and patients a right to inspect and obtain a copy of their PHI held by covered entities in what is termed a "designated record set." A designated record set includes any record that is maintained by the covered entity or its business associate that is a medical, billing, enrollment, or payment record or other record that is used to make decisions about the subject of the information. It may be, in some cases, that research data would not be considered part of the designated record set if, for example, the research data is not used to make decisions about the individual and not part of the medical record. In that case, the individual would not have a right to access the data, but this should be examined on a case-by-case basis with institutional officials. In the case of research that includes treatment, including clinical trials, the Privacy Rule permits a covered entity to suspend the individuals' access rights until the end of the research study, provided the individual agreed to the suspension when consenting to participate in the research and was informed that right of access would be re-instated upon completion of the research. The Privacy Rule permits the covered entity to insert in the Authorization form a statement by which the subject agrees to the suspension of right to access during the clinical trial and that informs the individual that the right to access will be reinstated upon completion of the research.

Covered entities are required to have policies and procedures for responding to access requests, and researchers that are workforce members of a covered entity may wish to coordinate any response to a subject's request with the medical records department, privacy officer, or legal counsel to ensure compliance with both the Privacy Rule and institutional policies.

Q: Does the Privacy Rule permit a researcher in a covered entity to make adverse event reports to the IRB during a research study, which includes visit dates, a subject's initials, and other identifying information?

A: The Privacy Rule permits PHI to be used or disclosed for adverse event reporting if the use or disclosure is, for example, (1) permitted by the individual's Authorization, (2) pursuant to a waiver or alteration of Authorization, (3) required by law, or (4) for permitted public health activities, which may include reports to persons who are subject to the jurisdiction of the FDA when the report concerns an FDA-regulated product for which the person has responsibility, e.g., sponsors or FDA-regulated IRBs. Where the Privacy Rule requires a covered entity to meet a minimum necessary requirement, researchers should work with their IRB, institutional officials, and research sponsors to develop an adverse event reporting process that uses as few identifiers as possible. For example, consider coding adverse event reports to de-identify data, for example, by using study numbers unrelated to the participant's name and indicating relevant dates as "day X of the study." Also note that while an Authorization need not explicitly list each of the multitude of uses and disclosures of PHI that will comprise the research study (so long as the Authorization describes the purpose of the research study and persons or classes of persons to whom the information may be disclosed in a meaningful and specific manner), covered entities may nonetheless wish to include specific language about adverse event reporting, if relevant, in the Authorization to more fully inform the individual.

Q: Does the Privacy Rule limit, to specific types of research studies, disclosures permitted as preparatory to research or for research on decedents' information?

A: No. The Privacy Rule does not limit the types of research studies that may rely upon the provisions for reviews preparatory to research or for research on decedents' information set forth at section 164.512(i). However, representations made to satisfy these provisions must include, among other requirements at sections 164.512(i)(1)(ii) and 164.512(i)(1)(iii), a statement that the use or disclosure of protected health information is "necessary for the research purposes."

Q: May a covered entity use or disclose PHI to locate or identify the whereabouts of a research participant (e.g., subjects who are "lost to follow-up")?

A: A covered entity is permitted to use or disclose PHI to identify or locate the whereabouts of a research participant during the study as long as the use or disclosure is not limited in the individual's Authorization (or "grandfathered" prior permission, if relevant) or waiver or alteration of Authorization. In addition, such use or disclosure is permissible if, for example, it is necessary for treatment of the individual or for a permissible public health purpose.

Q: Does the Privacy Rule apply to individually identifiable health information of non-U.S. citizens held or maintained by a covered entity?

A: Yes. All individually identifiable health information, including individually identifiable health information of non-U.S. citizens, is PHI when it is held by a covered entity, unless it is otherwise excepted from the definition of PHI at Section 164.501 of the Privacy Rule.

Q: I am a researcher, and my research data source is asking me to sign a business associate agreement. Is this necessary?

A: Business associates are persons who perform certain services for, or functions or activities on behalf of, the covered entity that require access to PHI, but who are not part of the workforce of the covered entity. If the data source is not a covered entity, no business associate contract is required because the Privacy Rule only applies to covered entities.

If the data source is a covered entity, whether a business associate contract is required depends on the services, functions, or activities that the researcher is providing to, or performing for, the covered entity. Researchers are not business associates solely by virtue of their own research activities (although they may become business associates in some other capacity, e.g., if de-identifying PHI on behalf of a covered entity). A business associate agreement will typically be a legally enforceable contract, so a researcher may wish to consult legal counsel before signing one.

NIH Publication Number 04-5495 February 2004

Appendix E

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ADVERTISING FOR STUDY SUBJECT RECRUITMENT GUIDANCE

I. Purpose

To describe activities and requirements for advertising for research subject recruitment.

II. Scope

Applies to all clinical site research personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, subinvestigator(s) and clinical research coordinators.

III. Background

Advertisements may be used during a clinical trial to assist in the recruitment of prospective subjects for a clinical investigation.

In accordance with:

Title 21 CFR 50.20—General Requirements for Informed Consent
Title 21 CFR 50.25—Elements for Informed Consent
Title 21 CFR 56.111—Criteria for Institutional Review Board (IRB) Approval of Research
Title 21 CFR 312.7—Promotion and Charging for Investigational Drugs
Title 21 CFR 812.20—Application for Devices
Food and Drug Administration (FDA) Information Sheet—Recruiting of Study Subjects
FDA Information Sheet—Guide to Informed Consent Documents
FDA Information Sheet—Payment to Research Subjects

IV. Procedure

1. The Principal Investigator (PI) or designee will meet with the Clinical Research Coordinator (CRC) or site manager to discuss research study recruiting needs and determine the type of advertisement to be used (print/audio/video).

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2. The CRC and designated clinical site research personnel, who are authorized to develop advertisements, will review the FDA/IRB accepted guidelines for advertisements prior to developing proposed advertisements.
3. Any and all advertisements should include:
 - a. The name and address of investigator and/or research facility
 - b. The condition under study and/or purpose of the study
 - c. A summary of the criteria used to determine eligibility
 - d. A brief list of participation benefits, if any
 - e. The amount of time or other commitment required of subjects
 - f. The location of the research
 - g. A person or office to contact for further information
4. Advertisements should not include:
 - a. Claims that the drug, biologic or device is safe or effective for the purpose of the investigation.
 - b. That the test article is known to be equivalent or superior to any other drug, biologic or device [21 CFR 312.7(a), 812.7(d)].
 - c. Terms which imply the receipt of newly marketed products already proven.
 - d. Promises of free medical treatment when intent is only to state that subjects will not be charged for taking part in the investigation
 - e. Emphasis of payment for participation
5. The PI or designee will submit the proposed advertisement to the trial Sponsor. No advertisement will be implemented without approval from the Sponsor and the reviewing IRB.
6. The PI or designee will submit the Sponsor-approved proposed advertisement to the IRB. No advertisement will be implemented without approval from the reviewing IRB.
7. Printed advertisement—a final copy will be submitted to evaluate the size of the type and other visual effects.
8. Audio or video advertisement—the wording (script) for the advertisement prior to recordings may be submitted. The final audio/video will also be submitted.

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9. A copy of all IRB-approved advertisements will be forwarded to the Sponsor and a copy will be maintained in the investigator's regulatory file.

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OBTAINING AND MAINTAINING IRB APPROVAL GUIDANCE

I. Purpose

Establish required standard procedures to obtain and maintain Institutional Review Board (IRB) approval.

II. Scope

Applies to all clinical site personnel involved in the implementation and coordination of clinical investigation.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, subinvestigator(s) and clinical research coordinators.

III. Background

Except as provided in 21 CFR 56.104 and 56.105, any clinical investigation, which must meet the requirements for prior submission to the Food and Drug Administration (FDA), shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of 21 CFR 56 [21 CFR 56.103].

IRB approval is required for all behavioral or biomedical research on human subjects to assure that the risks to subjects are minimal and reasonable in relation to expected benefits. The IRB serves to protect the rights, welfare and safety of research subjects.

The IRB will notify the investigator in writing of its decision to approve or disapprove the proposed research activity, or of modifications required securing IRB approval. If the IRB decides to disallow the research, it will include in the written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing [21 CFR 56.109 (d)].

The investigator should not implement any deviation from, or changes to the protocol without agreement by the Sponsor and prior review and documented approval from the IRB, except where necessary to eliminate immediate hazard(s) to trial subjects, or when the change(s) involves only

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logistical or administrative aspects of the trial (e.g., change in monitor(s), change in telephone number(s)) [ICH GCP 4.5.2].

IRB conduct-continuing review of research covered by federal regulations at intervals appropriate to the degree of risk, but no less than once per year [21 CFR 56.109 (e)].

In accordance with:

- Title 21 CFR 54.25—IRB
- Title 21 CFR 56.103—Circumstances in which IRB Review is Required
- Title 21 CFR 56.109—IRB Review of Research
- Title 21 CFR 56.111—Criteria for IRB Approval of Research
- Title 45 CFR 46.109—IRB Review of Research (if applicable)
- ICH GCP Consolidated Guideline—Part 4.4 Communication with IRB/EC
- ICH GCP Consolidated Guideline—Part 4.5.2 Compliance with Protocol

IV. Procedure

1. The Principal Investigator (PI) will submit all proposed clinical investigations for IRB review to an IRB designated and authorized by the research facility that complies with the requirements of 21CFR 56.
2. The PI will obtain written approval before any human subjects are allowed to participate in a clinical investigation except as provided in 21 CFR 56.104 (Exemptions from IRB requirement) and 56.105 (waiver of IRB requirement).
3. The PI is responsible for submitting all records to the reviewing IRB in a timely manner. The PI may assign the duty of record submission to appropriate clinical site research personnel. Records requiring IRB review include:
 - a. Protocol and any amendments
 - b. Investigator's brochure and any amendments
 - c. Consent form and any revisions
 - d. Copy of 1572 and any revisions
 - e. A report of prior investigations, if a medical device for human use
 - f. Advertisements to be used for subject recruitment
 - g. Other written materials to be provided to subjects
 - h. Any diaries, questionnaires or other materials the subject will be asked to complete

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- i. Safety reports, data safety monitoring boards (DSMB) reports and other such information
 - j. Serious adverse events (see SOP # CL 014).
 - k. Other documents as required by individual IRB (such as application forms, checklists, certificates of financial disclosure, etc.
 - l. Reports of any protocol deviations.
 - m. For studies that require biosafety review (gene therapy protocols), a copy of IBC Correspondence and Appendix M
 - n. Pre-IRB review documents as required by the IRB.
4. Continuing (annual) review will be submitted at least annually as required by the IRB. *Note: the IRB may require more frequent review of a protocol.* The annual renewal should be submitted in time to assure no lapse in approval. *(Example, if the IRB approves the study on Feb. 10 of this year, but the IRB will not meet until Feb. 14 next year, the annual renewal must occur in January to avoid the four-day lapse in approval).*
 5. The PI or designee will obtain IRB-specific reporting requirements and submit all reports accordingly.
 6. The PI or designee will maintain records of all submissions, correspondence and all actions by the IRB regarding the clinical investigation in the investigator's regulatory files *(and in a database).*
 7. The PI or designee will copy the trial Sponsor on all correspondence related to record submission to the IRB.
 8. If directed by the IRB, the consent forms will be revised in the event of new safety information that may impact subject willingness to participate in a trial. Only current, IRB-approved versions of consent forms will be utilized for obtaining informed consent.
 9. The PI or designee will submit all protocol amendments (and related consent form revisions) to the IRB for approval prior to implementation, except whereas to eliminate immediate hazard(s) to trial subjects.
 10. At the conclusion of a trial, the PI will complete and file a final report with the reviewing IRB.

Appendix G

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HANDLING IRB CORRESPONDENCE

I. Purpose

To provide guidance between the clinical investigational site and the Institutional Review Board (IRB) regarding necessary communication concerning clinical investigations.

II. Scope

Applies to all site personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, subinvestigator(s) and clinical research coordinators.

III. Background

The principal investigator (PI) is required to prepare and maintain adequate records of all correspondence to and from the IRB. All records should be readily accessible to the FDA, if requested for during an inspection.

Before initiating a trial, the investigator must have written IRB approval for the research protocol, consent form and any other written information to be provided to subjects. All documents subject to review must be submitted to the IRB on behalf of the responsible PI. IRB correspondence files contain copies of all such relevant communications and serve as an audit trail for a trial.

In accordance with:

Title 21 CFR 312.66—Assurance of IRB Review

Title 21 CFR 56.115—IRB Records

Title 21 CFR 812.140—Records

Title 21 CFR 812.150—Reports

Title 45 CFR 46.115—IRB Records (if applicable)

ICH GCP Consolidated Guideline—Part 4.4 Communication with IRB/IEC

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IV. Procedure

The PI will be responsible for all communication with the IRB concerning the investigation. The PI may assign clinical site research personnel the duty of communicating with the IRB and maintaining such correspondence.

IRB correspondence should include:

- Request for protocol and consent form approval

- Notification of revisions

- Notification of amendments

- Progress reports

- Notification of serious adverse experiences (SAE) from site/sponsor

- Notification of study closure/investigator's final report

- Any other report required by the reviewing the IRB bylaws.

The lead clinical research coordinator, site manager or designee will file all IRB correspondence in the investigator's regulatory file and submit copies to the trial sponsor.

Appendix H

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NEGOTIATING RESEARCH CONTRACTS GUIDANCE

I. Purpose

To document the process for completion of a clinical research site contract.

II. Scope

Applies to all clinical site research personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, sub-investigator(s) and Director/Site Manager, Legal Counsel, support personnel.

III. Background

The Principal Investigator (PI) or Site Director is responsible for negotiating and signing the clinical site agreement or contract. This activity is usually delegated to legal counsel to assure maximum protection afforded to the site regarding budget and indemnification language.

In accordance with:

Site Policies and Procedures
Local, State and Federal Laws

IV. Procedure

1. The Site Manager will forward to Legal the following:
 - a. Sponsor clinical site agreement or contract
 - b. Approved budget for site (note: legal can begin work on the contract without the final approved budget)
 - c. Contact list for the Sponsor's Legal department
 - d. Copy of the protocol and informed consent
 - e. Anticipated Institutional Review Board (IRB) review date
2. The Project Manager, Site Manager or designee will provide the legal counsel with any updates on the status of the trial and IRB approval.
3. Legal will complete a review of the contract and communicate any changes to the Sponsor's Legal department.

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4. Once a negotiated agreement is reached, legal counsel will provide the PI with the original(s) to sign.
5. Original documents will be sent to the Sponsor by a trackable route (FedEx, Airborne Express, etc.)
6. A copy of all legal correspondence is kept in the legal files for the study.
7. Legal will sign off on the signature line of the study sign-off sheet once the final executed contract is filed onsite.

Appendix I

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AMENDMENTS TO THE RESEARCH CONTRACT GUIDANCE

I. Purpose

To document the process for completion of an amendment clinical research site contract.

II. Scope

Applies to all clinical site research personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, sub-investigator(s) and Director/Site Manager, Legal Counsel, support personnel.

III. Background

Certain protocol amendments or addition of investigator's may necessitate a change or addendum to the site agreement or contract. This could include, but is not limited to, budget changes associated with amendments, indemnification of new investigators, change in Principal Investigator (PI), etc.

In accordance with:

Site Policies and Procedures
Local, State and Federal Laws

IV. Procedure

1. The Site Manager will forward to Legal the following:
 - a. Sponsor clinical site agreement or contract addendum template
 - b. Reason for renegotiation of contract along with pertinent details
 - c. Contact information for legal negotiations and completion of agreements
2. Once a negotiated agreement is reached, legal counsel will provide the PI with the original(s) to sign.

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3. A copy of all legal correspondence is kept in the legal files for the study.
4. Legal will notify the PI and Site Manager when a final executed document is filed onsite.

Appendix J

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LETTERS OF AGREEMENT GUIDANCE

I. Purpose

To document the process for negotiation and documentation of clinical services to support protocol required activities.

II. Scope

Applies to all clinical site research personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, when delegated by the investigator, Director/Site Manager, Legal Counsel, Departmental Managers.

III. Background

The Principal Investigator (PI) or Site Director is responsible for negotiating the services necessary for protocol required tests/procedures done by providers outside the site. This activity is usually delegated to management or legal counsel to assure maximum protection afforded to the site regarding budget and indemnification language.

In accordance with:

Written Protocol
Site Policies and Procedures
Local, State and Federal Laws

IV. Procedure

1. The Site Manager will review with the PI the following:
 - a. Protocol required tests/procedures
 - b. Those tests/procedures deemed standard of care and not paid for by the Sponsor will be billed to insurance or third party payers.
 - c. Those tests/procedures to be paid for out of the study budget will be itemized.
2. The Site Manager will negotiate with providers for those tests/procedures not done at the site.

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3. Once prices are negotiated, the Site Manager will prepare a document (letter of agreement) that outlines the services to be provided and the terms of financial compensation for each outside provider.
4. The letter of agreement will have signature lines for the Site Manager and the responsible person at the provider.
5. The Site Manager will obtain contact persons for billing from each provider. This will be provided to the site person responsible for tracking accounts payable and accounts receivable.
6. The Site Manager will provide the Clinical Research Coordinator (CRC) the list of approved providers for protocol required tests/procedures.
7. The CRC Clinical research coordinator may not schedule any test/procedure at another provider without the Site Manager obtaining a letter of agreement from that provider.
8. A copy of all letters of agreement and associated correspondence will be kept in the legal/budget files for the study.

Appendix K

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SERIOUS ADVERSE EXPERIENCE REPORTING GUIDANCE

I. Purpose

To provide a procedure for the accurate and timely reporting of serious adverse experiences (SAE) from the clinical site to the study sponsor. The sponsor's standard operating procedure (SOP) except when they conflict with federal regulations or other points of law may supercede this SOP.

II. Scope

Applies to all personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, when delegated by the investigator, sub-investigator(s) and clinical research coordinators.

III. Background

SAE reporting generally includes the report of any adverse drug experience or device effect observed during an investigation that is considered to be serious, regardless of causality or severity. The term serious is a regulatory definition as defined in the code of federal regulations whereby severity is a clinical definition. Principal investigators (PI) are obligated to report all SAE to both the Sponsor and to the IRB. Sponsors and IRB may have specific requirements and/or forms for reporting SAE that must be followed by clinical site research personnel.

Sponsors must report to the FDA and participating investigators all serious, expected or unexpected adverse experiences with the use of an investigational drug during a clinical investigation [21 CFR 312.32 (c)(4)(a)].

In the case of investigational drugs, if upon further evaluation of the SAE, the Sponsor determines that the investigational drug presents an unreasonable and significant risk to subjects [21 CFR 312.56 (d)], the

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Sponsor may:

- a. Discontinue the investigation and notify the FDA, IRB and participating Investigators that the study is being discontinued
- b. Assure FDA of the disposition of all outstanding stock of clinical trial material (CTM)
- c. Furnish FDA with a full report of its actions

In the case of devices, the sponsors must evaluate any unanticipated adverse device effect immediately [21 CFR 812.46 (b)] and report the results to the FDA, IRB and participating investigators within 10 working days after the Sponsor first receives notice of it [21 CFR 812.150 (b)(1)]. If the Sponsor determines that an unanticipated adverse device event presents an unreasonable risk to study subjects, the Sponsor will terminate part or all the investigation as soon as possible, but no later than five working days after the Sponsor made the determination and no later than 15 working days after the Sponsor first received notice of the effect [21 CFR 812.46 (b)(2)]. Sponsors must receive FDA and IRB approval to resume a terminated study of a significant risk device [21 CFR 812.46(c)].

SAE reporting is in accordance with the following regulatory requirements and industry guidelines:

- Title 21 CFR 312.32—RM Safety Reports
- Title 21 CFR 803, Subpart B—Generally Applicable Requirements for Individual Adverse Events Reports
- Title 21 CFR 812, Subpart G—Records and Reports
- Title 21 CFR 812.140—Investigational Device Exemptions—Records
- Title 21 CFR 812.150—Investigational Device Exemptions—Reports
- ICH GCP Consolidated Guideline—Part 4.11 Safety Reporting

IV. Procedure

1. The PI is responsible for reporting all SAEs to the trial Sponsor immediately except for those events that the protocol identifies as not requiring immediate reporting.
2. The PI is responsible for reporting serious adverse experiences to trial sponsors, however, he/she may delegate the data collection and communication of such events to appropriate clinical site research personnel. The PI and/or designee will:

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- a. Identify SAE
 - b. Report findings in the appropriate section of the case report form
 - c. Follow SAEs according to applicable regulations and report changes to the Sponsor, as required by protocol
3. The PI or designee will promptly report any serious and/or unanticipated/unexpected adverse experiences for drugs or biologics to the Sponsor and to the IRB in accordance with [21 CFR 312.64 (b)]. Unanticipated adverse experiences with investigational devices will be reported to the Sponsor and the IRB in accordance with [21 CFR 812.150(a)(1)].
 4. For reported deaths, the PI or designee should supply the Sponsor and IRB with any additional requested information (e.g., hospital records and autopsy reports).
 5. The investigator must notify the IRB of any safety reports from other research sites as received from sponsors.
 6. In the case of investigational drugs, if upon further evaluation of the SAE, the Sponsor determines that the investigational drug presents an unreasonable and significant risk to subjects [21 CFR 312.56 (d)], the Sponsor may require the PI to:
 - a. Discontinue the investigation
 - b. Notify the IRB and clinical site research personnel that the study is being discontinued
 - c. Return all outstanding stock of CTM
 7. In the case of devices, the investigator must immediately notify the Sponsor of any unanticipated adverse device effects [21 CFR 812.46 (b)]. If instructed by the Sponsor, the investigator should report the results to the IRB.
 8. The PI is responsible for immediately discontinuing a trial upon receipt of notification from the Sponsor in the event that the Sponsor determines that an unanticipated adverse device event presents an unreasonable risk to study subjects.
 9. In order to resume a previously terminated study of a significant risk device, the PI must submit a request to the reviewing IRB and copy all IRB correspondence/approval to the Sponsor.

Appendix L

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PRODUCT ADVERSE EVENT/DEVICE MALFUNCTION REPORTING GUIDANCE

I. Purpose

To establish the requirements and procedure for reporting adverse device effects or malfunctions (including breakage) at the clinical site.

II. Scope

Applies to all site personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, when delegated by the investigator, sub-investigator(s) and clinical research coordinators.

III. Background

Product adverse event/device malfunction reports include any undesirable, unexpected or breakage concerning the use of an investigational device/product regardless of causality or severity. This includes nonfunction, breakage or other such event.

In accordance with:

21 CFR 312.32—IND Safety Reports
21 CFR 312.64—Investigator Reports
21 CFR 314.80—Postmarket reporting of adverse drug experiences
21 CFR 812.3—Investigational Device Exemptions—Definitions
21 CFR 812.140—Investigational Device Exemptions—Records
21 CFR 812.150—Investigational Device Exemptions—Reports
ICH GCP Consolidated Guideline—Part 4.11 Safety Reporting

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IV. Procedure

1. The Principal Investigator (PI) will report all adverse experiences/device effects to research sponsors and the IRB. The PI may task clinical research coordinators with reviewing subject medical records for potential adverse experiences/product malfunctions as well as with entering the required information on the case report form (CRF). The responsibility for evaluation of the adverse experiences, however, remains with the PI.
2. Adverse experience information in the source document should include, but not be limited to):
 - Date of occurrence
 - Any related events (*what happened to the subject*)
 - Laboratory tests performed and results (if applicable)
 - Treatment(s)
 - Outcome
3. The PI will use his/her judgment as to the relationship between the study article and the adverse experience.
4. The PI and designees will refer to the study protocol for definitions, severity scoring systems and other reporting requirements as specified by the Sponsor.
5. The PI or designee will forward the report to the IRB, monitor or sponsor, as required by protocol or specific policies.
6. The PI or designee will save all equipment, catheters, etc. that malfunction/break and ship back to the Sponsor per instructions (this will be noted in the device accountability log per Sponsor instructions).

Appendix M

POLICY OF THE NATIONAL CANCER INSTITUTE FOR DATA AND SAFETY MONITORING OF CLINICAL TRIALS

Introduction

All clinical trials supported or performed by NCI require some form of monitoring. The method and degree of monitoring should be commensurate with the degree of risk involved in participation and the size and complexity of the clinical trial. Monitoring exists on a continuum from monitoring by the principal investigator/project manager or NCI program staff to a data and safety monitoring board (DSMB). These monitoring activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Throughout this policy, the term "awardee" means the awardee institution. In the case of NCI intramural research, the comparable institutional unit is the NCI.

Responsibility for Data and Safety Monitoring

Responsibility for data and safety monitoring depends on the phase of the study and may be conducted by NCI program staff or contractor, by the principal investigator/project manager conducting the study, or by a DSMB. Regardless of the method used, monitoring must be performed on a regular basis. Oversight of the monitoring activity is the responsibility of NCI program staff. In the case of extramurally funded research, adherence to this NCI policy and any data and safety monitoring policies of the NCI Division making the award will be made a condition of the award.

Phase I and Phase II studies may be monitored by the principal investigator/project manager, by NCI program staff or a designee, or jointly. When conducted by the principal investigator/project manager, the awardee must have written policies and procedures describing the monitoring and reporting processes in place. The awardee's policies must be consistent with any policies of the NCI Division making the award. NCI program staff from the awarding NCI division will determine the acceptability of the awardee's policies and procedures. These will be documented in the grant, cooperative agreement or contract file and become part of the award.

All Phase III randomized clinical trials supported or performed by NCI require monitoring by a DSMB. The organization, responsibilities, and operation of the DSMB are described below.

For studies co-funded with other NIH Institutes or Centers (IC), the lead NIH IC will be responsible for monitoring the study and establishing a DSMB if necessary. Oversight of the DSMB will be the collaborative responsibility of the lead NIH IC and NCI.

Requirement for Data and Safety Monitoring Boards

Data and Safety Monitoring Boards must be established to monitor all Phase III randomized clinical trials supported or performed by NCI. Funds to support the functions and operations of the DSMBs will be provided by NCI in a fashion to be determined by each NCI Division.

Responsibilities of the DSMB

1. Familiarize themselves with the research protocol(s) and plans for data and safety monitoring.
2. Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. The DSMB reviews trial performance information such as accrual information. The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
3. Review reports of related studies to determine whether the monitored study needs to be changed or terminated.
4. Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
5. Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. A copy of this information will be provided to the NCI Division Director or designee. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRBs.

Membership

The DSMB voting members will be appointed for a fixed term by the principal investigator/project manager or designee. Proposed DSMB members must be reviewed and approved by the awarding NCI Division Director or designee prior to their appointment. The Chair of the DSMB will be selected from among the voting members. Voting members of the DSMB should include physicians, statisticians, other scientists, and lay representatives selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology. Program and statistical staff from the NCI will be permitted to serve as non-voting *ex officio* members of the DSMB at the request of the NCI Program Director.

Voting members may be from within or outside the institution¹, but a majority should not be affiliated with the institution. Staff affiliated with the institution

who are members of the DSMB should view themselves as representing the interest of patients and not that of the institution. Voting members directly involved with the conceptual design or analysis of a particular trial must excuse themselves from all DSMB discussion of the particular trial and must not receive that portion of the DSMB report related to the particular trial.

Meetings

DSMB meetings will be held at least annually and more often depending on the nature and volume of the trials being monitored. Each meeting should be divided into three parts. First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus in the open session may be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session. Following this session, a closed session involving the DSMB members and the coordinating center/statistical office statistician(s) handling the trial should be held. The statistician(s) should present and discuss the outcome results with the DSMB. A final executive session involving only DSMB members should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

A written report containing the current status of each trial monitored, and when appropriate any toxicity and outcome data, should be sent to DSMB members by the coordinating center/statistical office allowing sufficient time for the DSMB members to review the report prior to the meeting. This report should address specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow up.

Recommendations from the DSMB

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the coordinating center/statistical office, trial investigator(s), NCI program staff and statisticians, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

DSMB recommendation(s) will be given to the trial principal investigator/project manager² with a copy provided to the NCI Division Director or designee. If the DSMB recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial principal investigator/project

manager must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator/project manager does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for disagreement. The trial principal investigator/project manager, DSMB Chair, and the NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and NCI staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of the NCI Division that made the award under which the trial is supported should be followed in regard to amending the protocol or changing the award.³

Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial principal investigator/project manager for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. **Any** release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to **any** non-member of the DSMB, except as indicated above in the Recommendations section, until the recommendation to release the results are accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

Conflict of Interest

DSMB members are subject to the awardee's policies regarding standards of conduct. Individuals invited to serve on the DSMB as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator/project manager and the appropriate institutional official(s), in accordance with the institution's policies. Conflict of interest can include professional interest⁴, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR

Part 94. Potential conflicts which develop during a member's tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution's policies.

¹ "Institution" is defined for this purpose as the awardee(s) institution and any institutions collaborating scientifically in the conceptual design or analysis of the study (beyond merely referring patients), including Cooperative Group member institutions participating in the trial, or consortia member institutions participating in the trial.

² "Trial principal investigator/project manager" means the individual primarily responsible for the project, i.e., the principal Chair of a Cooperative Group, the principal investigator listed on a U10, P01 or R01 award, or the project manager listed on a contract award.

³ This policy in no way affects any legal appeal rights of the awardee.

⁴ "Professional interest" is used in the sense of the trial outcome benefiting the individual professionally.

The above was approved by the NCI Executive Committee on [6/22/99](#).

Appendix N

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MANAGING PROTOCOL AMENDMENTS GUIDANCE

I. Purpose

To outline the process of handling protocol amendments at the clinical site so that change(s) in the protocol can be implemented.

II. Scope

Applies to all site personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, sub-investigator(s) and clinical research coordinators.

III. Background

Protocol amendments by the study Sponsor change or revise a protocol. There may be multiple amendments to a protocol throughout the duration of a trial. However, some protocols may not have any amendments.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval from the Institutional Review Board (IRB) of an amendment, except where necessary to eliminate immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change in telephone number(s)) [21 CFR 54.25 and ICH GCP 4.5.2].

In accordance with:

- Title 21 CFR 54.25—IRB
- Title 21 CFR 56.103—Circumstances in which IRB Required
- Title 21 CFR 56.109—IRB Review of Research
- Title 21 CFR 56.111—Criteria for IRB Approval of Research
- Title 21 CFR 312.30—Protocol Amendments
- Title 21 CFR 812.64—IRB Continuing Review
- Title 45 CFR 46.109—IRB Review of Research (if applicable)
- ICH GCP Consolidated Guideline—Part 4.4 Communication with IRB/IEC
- ICH GCP Consolidated Guideline—Part 4.5.2 Compliance with Protocol

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IV. Procedure

1. Upon notification of a protocol amendment, the Principal Investigator (PI) shall review the proposed change(s) and sign the amendment page if indicated, according to the sponsor policy.
2. The PI or designee will submit a copy of the protocol amendments to the IRB. No changes will be implemented without the approval of the reviewing IRB except to eliminate an apparent immediate hazard to study subjects.
3. The IRB submission package will include:
 - a. Cover letter from the PI to IRB
 - b. Protocol Amendment
 - c. Summary of changes
 - d. Revised Informed Consent Form (ICF) (if applicable)
 - e. Copy of FDA approval of amendment (Investigation Device Exemption (IDE) Letter for Device Study).
 - f. Any other material accompanying the amendment (revised Investigator Brochure, Instructions for Use, etc.).
4. The IRB will review and approve or disapprove the protocol amendment according to their written procedures and communicate approval or disapproval in writing to the investigator. Upon receipt of written approval (or disapproval), the PI or designee will submit a copy of the IRB letter and the signed protocol amendment page to the Sponsor.
5. A copy of the approved amendment will be sent to all subinvestigators and coordinators involved in the study.
6. A copy of the amendment will be reviewed by the Director or his designee to see if the amendment impacts the financial status of the study (i.e. the addition of protocol required tests or extending the follow-up period may require budget renegotiations).
7. All study documents containing information affected by the protocol amendment will be revised and submitted to the IRB for approval prior to implementation, if required, by the PI or designee. (Example: informed consent documents) These will be provided to all subinvestigators and coordinators involved in the study.
8. The PI or designee will inform all study subjects currently enrolled in the trial of any change or new information that may impact their

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decision to continue participation in the study. If the amendment changed the informed consent, all subjects will be reconsented.

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HANDLING SPONSOR, QA OR IRB-INITIATED AUDITS

I. Purpose

To describe the activities for facilitating a Sponsor or other investigational site audit.

II. Scope

Applies to all personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: Investigator/Co-investigator(s) and, *when delegated by the investigator*, sub-investigator(s), QA personnel and clinical research coordinators.

III. Background

Sponsors frequently audit investigational sites to inspect for protocol compliance and adherence to the U. S. Code of Federal Regulations, during or after the completion of a study.

Sponsors establish procedures for how site audits will be conducted. Site audits are likely:

- a. If there is high or low enrollment of study subjects
- b. If problems or concerns with the site have been reported by the monitor or
- c. Other responsible personnel
- d. If the study is one of extreme importance
- e. If the investigator's workload includes several studies with the same Sponsor
- f. If the geographic location of the site coincides with other sites being audited

In accordance with:

Title 21 CFR 312.62—Investigator Record Keeping and Record Retention for Clinical Drug or Biological Trials
Title 21 CFR 812.140—Investigator Record Keeping and Record Retention for Device Trials
ICH GCP Consolidated Guideline—Part 4.9 Records and Reports
ICH GCP Consolidated Guideline—Part 5.15 Record Access

Appendix P

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HANDLING MONITORING VISITS GUIDANCE

I. Purpose

To outline activities required for facilitating monitoring visits during the course of a clinical investigation.

II. Scope

Applies to all clinical site research personnel involved in the implementation and coordination of clinical investigations.

Personnel responsible: principal investigator (PI) and, *when delegated by the investigator*, subinvestigator(s) and clinical research coordinators.

III. Background

Sponsors conduct monitoring visits to ensure that investigators are compliant with the clinical protocol and good clinical practices (GCPs), that data are of high quality and integrity, and that the facilities and staffing are adequate for continued participation in the study.

In accordance with;

Title 21 CFR 52.47—Proposed Obligations of Sponsors and Monitors

Title 21 CFR 54.15—Proposed Obligations of Clinical Investigators

Guidelines for Monitoring of Clinical Investigations, 1988

ICH GCP Consolidated Guideline—Part 4 Investigator

ICH GCP Consolidated Guideline—Part 5.18 Monitoring

IV. Procedure

1. The lead CRC or Site Manager will schedule and arrange monitoring visits as requested by the Sponsor. Monitoring visits are conducted at intervals defined by Sponsor Standard Operating Procedures (SOPs) and often dependent upon enrollment. The first monitoring visit should be scheduled as soon as possible after the first two patients are enrolled into the trial. The dates of monitoring visits should be scheduled at mutually convenient times and every attempt should be made to accommodate monitoring deadlines. Participants will include

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the PI and subinvestigators whenever possible, and the CRC(s) and other ancillary staff as appropriate.

2. The lead CRC or Site Manager will schedule appointments with the PI, subinvestigators, Pharmacist and other clinical site research personnel as appropriate.
3. The lead CRC or Site Manager will provide notice to all clinical site research personnel, including regulatory that the Sponsor will conduct a monitoring visit at the site.
4. If requested by the sponsor, the lead CRC or Site Manager will schedule a tour of the facilities to be conducted during the monitoring visit. The tour should again establish that the necessary equipment is available, that there is continued adequacy of space to conduct the study, and that there is a secure, limited access area for study supplies and clinical trial material storage.
5. Prior to the monitoring visit, the lead CRC will confirm with the Sponsor Representative which cases will be reviewed so appropriate documentation and files can be obtained.
6. The lead CRC will ensure that all available requested study subject source documents and CRFs are provided for monitor review.
7. The Regulatory Affairs personnel will review the regulatory books and complete all filing prior to the monitoring visit.
8. The lead CRC will ensure that an appropriate work area is available for the Monitor during the monitoring visit. Monitors from different sponsors should not work in the same area. Discussions between monitors and staff will be done privately.
9. The lead CRC or Designee will accompany the monitor to the clinical trial material (CTM) storage area and will be available to assist with product accountability review if requested by the Sponsor.
10. Monitors must be accompanied at all times in storage areas.
11. Monitors are not allowed into drug cabinets or device storage areas to inventory. If necessary, clinical research staff will pull investigational drugs or equipment from the storage area for the Monitor to count.

Appendix P

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This is to maintain the confidentiality of other sponsor's investigational drugs or devices located in the same storage area.

12. The CRC(s) will schedule for time to work with the Monitor during the monitoring visit to review and complete any data clarifications as necessary.
13. CRFs and study related documents would be submitted to the Sponsor according to Sponsor SOPs. If copies of source documents are to be submitted to the Sponsor, then all subject-identifying information (name, except for initials, medical record number, account number) must be blacked-out to protect patient confidentiality. The Patient's study number or ID code will be written on the top of each document copied by the Monitor.
14. Prior to the end of the monitoring visit, Regulatory will review with the Monitor the Master log of all MedWatch or Safety Reports from other sites in order to make sure that the site has received all documents. If any reports are missing, the Regulatory personnel will request the Monitor provide a copy to the site as soon as possible. The Regulatory personnel will document this in a note to file.
15. The PI or Designee should acknowledge in writing receipt of Sponsor reports, if applicable, and note steps taken to correct any deficiencies.

Helpful Notes:

An appropriate work area for a Monitor should include a desk or work table that has ample space to lay out case books and patients' records. The Monitor should have access to a photocopy machine and telephone.



Administrative and Operational Policies and Procedures

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Policy Number:	1.16	Original Date Issued:	April 16, 2001
Section:	Operations	Date Reviewed:	June 6, 2007
Title:	Institutional Review Board Standard Operating Procedures	Date Revised:	June 6, 2007
Regulatory Agency:	FDA, DHHS, TJC		

I. POLICY:

Children's Healthcare of Atlanta, Inc., (Children's) protects the rights and welfare of human research subjects recruited to participate in research activities.

These Standard Operating Procedures for the Children's Institutional Review Board should be followed in conjunction with Children's Policy Number 8.15 entitled "Uses and Disclosures for Research Purposes & Waivers (HIPAA Research Policy)".

II. PROCEDURE:

Background Information

The Children's Audit and Compliance Committee of the Board in conjunction with Children's Administration assigns the responsibility for the protection of human subjects involved in research activities to the Children's Healthcare of Atlanta Institutional Review Board (IRB). The IRB will operate in compliance with hospital research policy(ies) and with the U.S. Code of Federal Regulations, Department of Health and Human Services (DHHS) Title 45 Part 46, entitled "Protection of Human Subjects", as well as the Food and Drug Administration (FDA) Title 21, Part 50 and Title 21 Part 56. A copy of the DHHS and FDA regulations may be obtained in the IRB Office.

The IRB's primary concerns in all its deliberations are to determine that:

- The rights and welfare of the subjects are protected adequately.
- The risks to subjects are outweighed by the potential benefits of the research.
- The selection of subjects is equitable.
- Informed consent will be obtained and documented.

Definitions

1. **Institutional Review Board:** A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research (CFR 46:102(g), 46:108, 46:109)



2. Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (CFR 46:102d)
3. Human Subjects: Living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. (CFR 46:102f)
4. Intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes.
4. Interaction includes communication or interpersonal contact between investigator and subject.
6. Private Information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (i.e., medical record). Private information must be individually identifiable (i.e. the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45CFR 46:102f(2))
7. Minimal Risk: 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 examination or tests. (CFR46:102i)
8. Informed Consent: A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence. (CFR 116:21, CFR 50.20 and 50:25)
9. Assent: Agreement by an individual not competent to give legally valid informed consent
10. Expedited Review: Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk or for minor changes in approved research.



11. Emergency Use: The use of a test article on a human subject in a life threatening situation in which no standard acceptable treatment is available and which there is not sufficient time to obtain IRB approval.

III. GENERAL INFORMATION

- A. Children's requires that all research projects involving human subjects be reviewed and approved by an IRB according to policies at the site where the research will be conducted.
- B. All research proposals submitted to the IRB must designate an institution medical staff member or employee as the principal investigator or co-principal investigator. The institution requires that responsibility for compliance with institutional research policies and guidelines rest with the principal investigator.
- C. The IRB is charged with the responsibility for review and approval of human subjects research conducted by or under direction of any full-time or part-time employee or agent of the institution and research involving patients and/or employees.
- D. Review and approval is required regardless of source (or lack of source) of funding for a project and regardless of the site at which the research is performed.
- E. These Standard Operating Procedures may be revised by the IRB subject to federal regulations and the approval of the Children's Audit and Compliance Committee of the Board or their designee.
- F. The Standard Operating Procedures will be given to all members of the IRB when they are appointed and to any medical staff or other researcher upon requesting to conduct research within Children's.
- G. The IRB is responsible for conducting Continuing Reviews on its approved research projects at least annually.
- H. The IRB is responsible for reviewing all serious adverse events and unanticipated risks on its approved projects.
- I. The IRB is responsible for reviewing and approving all modifications to its ongoing research projects.

IV. STATEMENT OF ETHICAL PRINCIPLE

Children's, including the IRB, will be guided by the ethical principles governing all research involving human subjects that are set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The Belmont Report)*. Researchers must agree to abide by these principles and the recommendations of the IRB. Instances of serious or continuing non-compliance with this policy or the requirements of the IRB will be reported to the appropriate authorities for investigation and resolution and where appropriate, the financial sponsor and/or federal authority.



V. COMMITTEE INFORMATION

- A. The responsibility for maintaining the IRB rests with the Senior Vice President, Medical Affairs.
- B. The Chairperson for the IRB will be appointed by the Children's Audit and Compliance Committee of the Board or their designee.
- C. The responsibility for appointing and maintaining IRB membership rests on the Children's Audit and Compliance Committee of the Board or their designee in consultation with the Chairperson.
- D. A Vice-Chair may be appointed by the Chair to assist with his/her duties.
- E. The IRB must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members and the diversity of their backgrounds, including considerations of their racial and cultural heritage and their sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. Composition of the IRB will be at least one member whose primary concerns are in scientific areas, one member whose primary concerns are in nonscientific areas, one member who is not affiliated with the institution and not part of the immediate family of a person who is affiliated with the institution.
- F. No member of the IRB shall be permitted to participate in the initial or continuing review of any project in which that member has a conflicting interest, except to provide information requested by the IRB. Each member must sign an IRB member recusal agreement form upon membership.
- G. All IRB written notifications are reviewed, approved and signed by the Chair. The Chair may designate this function to the Vice Chair or Administrative Manager as appropriate.
- H. With the exception of community members, all IRB members must pass an approved Human Subjects Protections Program and provide the IRB with a copy of the certification.

VI. MEMBER LIST

- A. A record of the names, degrees, qualifications, affiliation and voting status of the members of the IRB will be maintained.
- B. The record represents the roster of members and will serve monthly as the list by which attendance is determined.
- C. New appointments, dismissals, termination of appointments, and withdrawals of members will be noted on this roster and will be included in the meeting agenda and minutes.
- D. A copy of the current IRB membership list may be obtained from the Research Department, the Children's intranet site or the Children's public website.



VII. MEETINGS

- A. Meetings shall be scheduled on the fourth (4th) Thursday of each month unless otherwise noted on the published annual meeting schedule.
- B. Sufficient materials for review of each project shall be distributed to members at least two (2) weeks prior to each scheduled meeting.

VIII. QUORUM

- A. A quorum shall consist of 50% plus one (1) voting member(s) of the full IRB but must include one (1) member whose background or profession is in a scientific area, at least one (1) member whose background or profession is a non-scientific area, and at least one (1) community member.
- B. Quorum requirements must be met to convene a meeting.
- C. Only those members who are actually present at a meeting or available by conference call shall be counted toward a quorum and permitted to vote on the acceptability of a proposed study.
- D. Each member shall have one (1) vote for rendering decisions upon those research projects that come before the IRB for review and approval.

IX. CONFIDENTIALITY OF IRB MEETINGS AND RECORDS

All information related to IRB meetings, actions, and other business is confidential, including, but not limited to:

- A. Proceedings of convened meetings of the Institutional Review Board, are confidential and not to be discussed outside of the meeting. IRB members will, at all times, maintain the confidentiality of the process and not discuss individual proposals outside of the IRB meetings with individuals or parties who may inquire.
- B. Individual members of the IRB will not make independent statements regarding IRB matters and are not authorized to individually speak for the IRB or on its behalf.
- C. Institutional Review Board files and records are confidential and available only to sponsoring/funding agencies, the US food and Drug Administration, the Office for Human Research Protections, or other agencies with the Public Health Service / Department of Health and Human Services, or institutional officials or their appointees who may be conducting internal audits for compliance purposes.
- D. Only the Institutional Review Board Office, housed in the Research Department, may disclose the approval status of a particular proposal. Other information

requested by a source outside of those persons/ agencies referred to in section C. above, shall make their request to the Principal Investigator.

X. RECORDS

- A. The IRB should prepare and maintain adequate documentation of its activities regarding each research project to include the following:
 - 1. Complete copy of original application packet.
 - 2. Copies of all correspondence between IRB and investigators.
 - 3. Copy of Approval Notice.
 - 4. Copy of Reviewer's Analysis Sheet
 - 5. Copy of approved informed consent document.
 - 6. Continuing Renewal Request and Approval for Continuation.
 - 7. Modifications and copy of Modification Approval.
 - 8. Investigator's Brochure (when appropriate).
- B. Copies of agenda and minutes for each meeting to include attendance.
- C. The IRB shall retain the records required by these procedures regarding each research project for a period of at least three (3) years after research is completed, terminated or discontinued. The records shall remain accessible for inspection and copying by authorized representatives of appropriate regulatory bodies at reasonable times and in a reasonable manner.

XI. RECEIPT OF PROTOCOL BY IRB

- A. All applications must include the appropriate documents for each protocol as outlined below:
 - 1. IRB Submission Form
 - 2. Lay Summary - Optional
 - 3. Full Protocol
 - 4. Informed Consent
 - 5. Statement of Investigator (FDA Form 1572)
 - 6. Investigator Brochure
 - 7. Questionnaires or Data Collection Forms that are not standard published forms.
 - 8. Recruiting material
 - 9. Advertisements
 - 10. Copies of CITI course completion certificates. (Renewals of the refresher course are due every 2 years).
- B. On receipt of the application the IRB will assign a receipt date and IRB number. All future correspondence will reference the abbreviated title and assigned IRB number.
- C. An administrative review will be conducted to ensure completeness of the application. If the application is incomplete the principal investigator will be

notified and requested to appropriately complete the application. An incomplete application will not be processed by the IRB.

XII. DETERMINATION OF REVIEW PROCEDURE TO BE FOLLOWED

- A. The IRB Chairperson or his/her designee will determine whether the research protocol meets the criteria necessary for full review, expedited review, re-review or administrative review. Since this institution serves children, a vulnerable population, as outlined by DHHS, research that meets regulatory requirements for the exempt category will receive expedited review.

XIII. CATEGORIES OF REVIEW

A. FULL COMMITTEE REVIEW

NOTE: All research activities on human subjects require full board review unless the research meets the criteria for Expedited Review.

1. Protocols requiring full committee review must be in the IRB Office three (3) weeks prior to the next scheduled meeting.
2. One complete application is retained in the IRB Office and placed in the respective IRB numbered file.
3. The remaining copies are routed to the board members with a corresponding Reviewer's Analysis Sheet and informed consent checklist two-weeks prior to the meeting.
4. Each reviewer reviews the application, completes the Reviewer's Analysis Sheet and uses the Informed Consent Checklist as a guide to ensure completeness of the informed consent.
5. The Primary Reviewer for the submission considers the potential risks posed by the research procedures as s/he conducts the review and this is discussed during the convened IRB meeting.
6. At least one member of the Board reviews the Investigator's Brochure.
7. At the convened meeting the Chairperson references the application and discussion is opened to all members.
8. Disposition of an application is by majority vote.
9. Each reviewer completes and signs the Reviewer's Analysis Sheet indicating the following:
 - a. Approval, approval pending minor modifications, table pending major concerns or modifications, or disapproval.
 - b. Risk level of protocol.
 - c. Indicate time interval for Continuing Review
 - d. The Analysis Sheets becomes part of the IRB permanent file.
10. The investigator receives written notification of the IRB determination.
11. Upon final approval by the IRB, the principal investigator receives a Notice of Approval.



B. EXPEDITED REVIEW

1. Under federal regulation certain types of research are eligible for expedited review. *Only the IRB, and not an investigator acting independently*, determines whether a protocol meets the criteria for expedited review. The IRB may use an expedited procedure to review research that involves no more than minimal risk to the subjects and in which the only involvement of human subjects is outlined in the Expedited Review Category. (Attachment A)
2. Research proposals meeting criteria for Expedited Review are not subject to the IRB submission deadline.
3. Expedited review is conducted by the Chairperson or by one or more of the IRB members designated by the Chairperson.
4. Each reviewer completes a Reviewer's Analysis Sheet, which becomes part of the IRB permanent file.
5. The Chairperson or designee(s) conducting the review may exercise all of the authorities of the IRB except that they may not disapprove the research. They refer any research protocol that they would have disapproved to the full Board for review.
6. When the expedited review procedure is used, the proposal is placed on the agenda for the next convened meeting and the Chairperson notes they have been approved under this procedure.
7. At a convened IRB meeting, any member may request that any activity that has been approved under this procedure be reviewed by the IRB in accordance with non-expedited procedures. Under these circumstances, either a formal motion to approve the protocol will be noted on the minutes or the protocol will be suspended pending further review by the Chairperson or full Board.
8. Upon approval by the IRB, the principal investigator receives a Notice of Approval indicating that the expedited procedure was utilized.

C. EXEMPT CATEGORY

1. Currently the Federal human subjects protection regulations (CFR 45:101b) define certain types of human subjects research as Exempt from IRB review. (Attachment B)
2. Considering that children are a vulnerable population, the IRB policy is that no research is exempt from review and therefore will process this category of research using the Expedited procedure. (See Section X,B,1)

D. CHART OR MEDICAL RECORD REVIEW

1. Studies involving review of Children's patient charts or records, whether by principal investigator at Children's or from an institution other than Children's must be submitted to the Children's IRB and will receive an expedited review



2. The Children's IRB provides the investigator with a Notification of Approval and provides HIS (Health Information Services/Medical Records Department) a copy of the Request for Chart Review and the Notification of Approval.
3. Once the Notification of Approval is issued, the investigator reviews charts in accordance with the HIS policies.

D. ADMINISTRATIVE REVIEW

1. Changes/amendments to protocols that are only of an administrative nature and do not involve patient care or intervention may be reviewed and approved by the IRB Administrator, if so designated by the Chair.

XIV. IRB REVIEW PROCESS

- A. In order to approve a protocol the IRB shall determine that the following requirements are satisfied as appropriate to the protocol:
1. The risks to the subjects are minimized.
 2. The risks to the subjects are reasonable in relationship to anticipated benefits and the importance of the knowledge that may reasonably be expected to result.
 3. The selection of subjects is equitable.
 4. A process has been established for obtaining informed consent from each prospective subject or the subject's legal representative, in accordance with and to the extent required by DHHS and FDA regulations and the policies of the hospital.
 5. A process has been established to document informed consent.
 6. A procedure has been established to monitor the data collected to ensure the safety of subjects; and
 7. The investigational research plan adequately provides for the protection of privacy of subjects and the maintenance of confidentiality of data concerning those subjects.
 8. That applicable regulations for the protection of children (CFR 45: 46, Subpart D) are satisfied.
- B. The IRB may take into consideration, in its review of the proposed research, any prior approvals or disapprovals by other institutional review boards at other institutions. The IRB, however is in no way bound by these approvals or disapprovals.

XV. INFORMED CONSENT

- A. General Considerations
1. Whenever it is proposed during an investigation to perform any procedure involving any risk to a subject, informed consent should be

obtained and documented. An investigator should seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject shall be in a language understandable to the subject or representative. No such informed consent, oral or written, should include any exculpatory language through which the subject is made to waive, or appear to waive, any of his/her legal rights, including any release of the investigator, the sponsor, or the institution, and its agent from liability for negligence.

Regulations permitting waiver of informed consent can be found at 45CFR46:116 and 21CFR50.23

2. The information provided to the subject or the subject's representative shall be written in language understandable to the layperson and shall include at least the following:
 - (a) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
 - (b) A description of any reasonably foreseeable risks or discomfort to the subject and the precautions that will be taken to minimize those risks.
 - (c) A description of any benefits to the subject or to others which may reasonably be expected from the research.
 - (d) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
 - (e) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and the possibility that the FDA may inspect such records.
 - (f) An explanation as to whether any compensation for participation will be provided and whether any medical treatment will be available if injury occurs. If medical treatment will be available, the subject must be advised as to what it consists of or where further information may be obtained.
 - (g) An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury.
 - (h) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

B. Additional Elements of Informed Consent:

When appropriate the following information shall also be provided to each subject:

- (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are unforeseeable.
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without his or her consent.
- (3) Any additional costs to the subject that may result from participation in the research.
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject on a timely basis.
- (6) The approximate number of subjects involved in the study.

C. Obtaining Consent

1. An adult with decision-making capacity will be responsible for determining if he/she will participate in the investigation.
2. Where a clinical investigation involves minor patients as subjects or adult patients without decision-making capacity, the signature of at least one parent will be required. If the protocol or research holds more than minimal risk to the patient and does not hold a prospect of providing direct benefit to the patient and will likely yield generalized knowledge about the subject's disorder or condition which is of vital importance, consent of both parents is needed, unless, in accordance with the provisions of 45 CFR 46.408(b) one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
3. The "assent" of a minor patient will be sought by the investigator if the patient is of sufficient maturity to understand the risks, benefits, alternatives, and implications of the research. The investigator will determine if assent is appropriate. If the assent is not obtained, the investigator should document the reasons why on the consent form. NOTE: If a minor patient refuses to assent, a referral to the Ethics Committee is recommended.



4. Where the clinical investigation involves pregnant women or fetuses as subjects, the signature of both parents is required, except that, in accordance with the provisions of 45 CFR 46.208(b) and 46.209(d): the father's whereabouts cannot reasonably be ascertained; he is not reasonably available or the pregnancy resulted from rape.

D. Consent Form Requirements:

1. A consent form shall be developed for each protocol and maintained for each subject. The consent form shall contain all information required by the FDA and the IRB and any other information deemed necessary to insure that the subject is properly informed and protected. The original consent will become a permanent part of the subject's research record and a copy will be placed in the subject's medical record.

XVI. IRB DISPOSITIONS

A. Final Approval

1. The principal investigator will receive a written Notice of Approval from the IRB.
2. The protocol may not be initiated until the principal investigator receives the Notice of Approval.
3. The Notice of Approval will inform the investigator of the approval date, the approval period, the approval type (full committee or expedited), requirement for continuing renewal, requirement for approval of modifications, requirement for prompt reporting of adverse events, requirement of maintaining appropriate records, requirement that all staff involved in the research are informed and trained, and the IRB approved informed consent will be attached.

B. Approval Pending Modifications

1. Protocols that can be approved pending non-substantive clarifications of the protocol and/or minor revisions in the informed consent are in this category.
2. The principal investigator will be notified in writing from the IRB what clarifications of the protocol or what revisions in the informed consent are requested.
3. The letter will state the research may not commence until the investigator receives a Notice of Approval from the IRB.
4. The principal investigator replies to any IRB correspondence within 90 days of receipt of the IRB correspondence. If there is no reply within this period, the pending file will be deactivated by the IRB and the investigator will be notified that the protocol has been withdrawn from

consideration. Deactivated protocols are re-submitted as a new protocol. (see Section XXV for exception to this rule)

5. Upon receipt of the clarifications or revisions the IRB Chairperson or his/her designee may grant final approval.
7. The principal investigator will receive a written Notice of Approval from the IRB.
8. The protocol may not be initiated until the principal investigator receives the Notice of Approval.

C. Tabled or Re-Review

1. Protocols with which the reviewers have substantive questions and about which there are concerns about protocol design, risks, and/or the informed consent will be reserved for this category.
2. The principal investigator will receive a written communication regarding these concerns.
3. The investigator must reply within ninety (90) days of the date of the IRB correspondence. Failure to reply within this time frame will result in the IRB deactivating the protocol. Should the investigator respond after the ninety (90) day deadline he/she will be informed that the must submit the protocol as a new submission.
4. The investigator's reply will be provided to each IRB member and placed on the agenda for the next convened meeting.
5. Each IRB member will determine if all issues and/or concerns have been adequately addressed and all requested revisions have been made.
6. The IRB member will indicate on the review form one of the following:
 - a. The protocol is now approved.
 - b. Minor revisions are still needed
 - c. Issues/concerns have not been adequately addressed.
7. The protocol will be placed on the agenda for the next convened meeting.
8. When the re-review is discussed the IRB may give final approval, approve pending minor revisions, disapprove the protocol, or vote to re-review.
9. The investigator will receive written communication regarding the IRB's disposition.
10. If the IRB determines that more information is necessary before giving final approval, the principal investigator may be invited to attend the next convened meeting to present, in response to the concerns, a reply and defense of the protocol.
11. After an open discussion, the investigator will leave the meeting and the IRB will vote.
12. The protocol will receive full approval, pending approval, or disapproval by majority vote.
13. The IRB disposition will be communicated to the investigator.

D. Disapproval

1. The IRB shall disapprove, or may suspend or terminate, research protocols involving human subjects if it finds that:
 - a. The information submitted to the IRB by the investigator contains any untrue statement material to the IRB's decision making or omits information required by the IRB to review and evaluate the research that has been proposed.
 - b. The report of prior investigations is inadequate to support a conclusion that it is reasonably safe to initiate or to continue the investigation.
 - c. The principal investigator does not possess the scientific training and experience to qualify as an expert to investigate the safety and/or effectiveness of the test drug or medical device.
 - d. The available clinical laboratory facilities and/or the medical support are inadequate to assure that the investigation will be conducted properly and in conformity with the proposed protocol.
 - e. The investigational research does not conform to and/or is not being conducted in accordance with the approved protocol and/or the requirements of the FDA and the institution pertaining to human subject research.
 - f. The investigations research exposes or may expose subjects to undue risks. In assessing such risks, the IRB shall consider, among other factors, all of the following:
 1. whether the risks to the subject are so outweighed by the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to approve the research and thereby allow the subject to accept the risks;
 2. whether the rights and safety of the human subjects will be adequately protected;
 3. whether informed consent will be obtained by adequate and appropriate methods in accordance with applicable requirements governing such research;
 4. whether the proposed investigation will be or is being reviewed by the sponsor and/or by the IRB, as appropriate, at intervals appropriate to the degree of perceived risk.

E. Withdrawal of Protocol

1. An investigator may withdraw his/her protocol at any time prior to the IRB granting final approval. The IRB will place the file in the Protocols Withdrawn file upon receipt of a withdrawal notice from the investigator



2. If the IRB has granted final approval the investigator must terminate the protocol by completing a Continuing Renewal Request

XVII. APPEAL PROCESS

- A. When the IRB maintains disapproval of a protocol after initial review, second review including the investigator's comments and reply to the IRB's first disapproval and third review with the principal investigator in attendance at the convened meeting, the investigator may then submit an appeal of the final IRB disapproval to the Senior Vice President, Medical Affairs, with appropriate explanations. The Senior Vice President, Medical Affairs will seek expert opinions on the protocol from individuals within or from outside institutions. These opinions will be submitted to the full IRB for review. The IRB will reconsider the protocol in view of the expert opinions, vote on the protocol, and report its conclusion to the investigator and the Senior Vice President, Medical Affairs.
- B. Approval by the IRB of research protocols may be subject to further appropriate review by the Senior Vice President, Medical Affairs. However, the Children's Audit and Compliance Committee of the Board or their designee shall not overrule disapproval of such a protocol by the IRB. The IRB's decision to disapprove a protocol will be communicated to the investigator in writing and will include the reasons for disapproval.

XVIII. SUSPENSION OR TERMINATION OF IRB APPROVAL OF RESEARCH

- A. The IRB has authority and retains the right to suspend or terminate approval of any research protocol in its discretion, including, but not limited to, a research protocol which is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.
- B. Any suspension or termination of approval shall be reported to the investigator the Children's Audit and Compliance Committee of the Board and where appropriate, the sponsoring agency.
- C. If the IRB decides to suspend or terminate a research protocol, it shall include in its order, provisions regarding any subject who has previously been allowed to participate in the protocol and who either would have continued to receive the test article or who remains under the supervision of the investigator. Such provisions shall take into account among other factors, the risks to the subject from the withdrawal of the test article or from its continued administration by another physician, the need for further medical supervision, the availability of qualified medical personnel, and the rights of the subject to include the right to participate in the decision as to future care.

XIX. CONTINUING REVIEW

- A. The IRB shall continue to review a research protocol that has been approved, until the protocol is concluded or discontinued. The length of time before IRB continuing review needs to occur is determined by the IRB at initial review.
- B. The Continuing Review shall be undertaken at intervals appropriate to the degree of risk as determined by the IRB, but shall not be less often than once per year, to assure that the protocol is being conducted in compliance with the requirements and understanding of the IRB and all applicable regulations.
- C. The IRB shall provide the investigator with a Continuing Renewal Request 30 days prior to the initial approval date or last continuing approval date.
- D. Continuing Renewal Requests are subject to the IRB deadline date of three (3) weeks prior to the next convened meeting.
- E. Continuing review of research previously approved using the expedited process will be reviewed using the expedited process.
- F. Continuing review of research previously approved by the convened IRB will be reviewed using the expedited process as follows:
 - 1. where (a) the research is permanently closed to the enrollment of new subjects; (b) all subjects have completed all research-related interventions; and (c) the research remains active only for long-term follow-up of subjects; or
 - 2. where no subjects have been enrolled and no additional risks have been identified; or
 - 3. where the remaining research activities are limited to data analysis.
 - 4. research not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) (in Attachment A) do not apply but the IRB has determined at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.
- G. All other continuing review requests will be reviewed at a convened meeting.
- H. The IRB reserves the right to perform an on site review. This may include a Board member(s) observing the informed consent process, reviewing the study records and documenting that the approved informed consent is being utilized.
- I. If the investigator fails to respond to the Continuing Renewal Request by its due date all research activities must cease until approved for continuing renewal by the IRB.
- J. Failure by the investigator to respond to the Continuing Renewal Request within 30 days after the renewal due date will result in the termination of the protocol. If the investigator wishes to continue, he/she must submit for continuing renewal.

XX. TERMINATION REPORTS

- A. An investigator is responsible for notifying the IRB when a protocol has been terminated using the Continuing Renewal Request



- B. If the investigator does not report the termination he may do so when he receives the next Continuing Renewal Request.
- C. When a protocol has been terminated the IRB file will be placed in the inactive files and if an investigator wishes to re-instate the protocol he must submit a new application to the IRB.

XXI. MODIFICATIONS TO PROTOCOLS AND REVISIONS TO INFORMED CONSENTS

- A. The investigator is required to provide the IRB a Modification Form indicating any proposed revisions and amendments to the research protocol and any proposed revisions to the informed consent necessitated by amendments to the protocol or by the generation or receipt of new information, including that from adverse event reports.
- B. Any such proposed changes in the protocol or informed consent must be approved by the IRB before implementation or use by the investigator.
- C. The Chairperson or his/her designee will review all amendments to protocols and revisions to informed consents and determine whether the proposed changes are substantive. Minor changes will be considered under the Expedited process and the proposal will be placed on the agenda for the next convened meeting.
- D. If the proposed change(s) is/are judged by the IRB Chairperson or his/her designee to be substantive, the proposal must be reviewed by the full IRB and approved before the change can be implemented. Substantive changes include procedures involving increased or different risks, additional discomforts, or new procedures.
- E. Unanticipated risks may be discovered during the course of a protocol, or new information indicating that the risks in a protocol are not justified may be discovered. Unanticipated risks or new information that may affect the risk/benefit ratio must be promptly reported to and reviewed by the IRB to insure adequate protection of the welfare of the subjects. Based on such information, the IRB may reconsider its approval of the protocol or institute new conditions for continuation and review.
- F. The IRB will provide written approval of all modifications to the investigator. In cases where the informed consent requires revisions, a copy of the informed consent indicating IRB approval with the approval date will be provided to the investigator.

XXII. ADVERSE EVENTS

- A. Any adverse experiences and unexpected events in the conduct of the protocol must be promptly reported by the investigator to the IRB, but not later than ten (10) working days after the occurrence. This includes adverse experiences that occur at other institutions which the sponsor reports to the investigator at this Institution.
- B. A Serious Adverse Event Report must be completed with a written narrative that includes sufficient detail for a thorough review by the IRB.



- C. Failure to report an occurrence in a timely manner may result in temporary or permanent suspension of the protocol.
- D. The Chairperson or his/her designee will review each report of an adverse event and will determine whether the report requires action.
- E. If the reported event is deemed non-substantive or not due to the drug, device, or protocol, the adverse event will be placed on the agenda for the next convened meeting, discussed and recorded in the minutes.
- F. If it is determined that the event requires further action, additional information or merits discontinuation of the protocol, the Chairperson will immediately contact the investigator and Children's Audit and Compliance Committee of the Board or its designee and suspend the protocol if warranted, or further investigate the event.

XXIII. OTHER REPORTS

- A. The investigator must provide the IRB any other reports that have bearing on the review of the protocol, such as Investigational New Drug (IND) Safety Reports, in the same or similar protocols recorded by the investigator or others at other institutions. Copies of the reports are generally provided to the investigator by the sponsoring agency and must be submitted to the IRB promptly.
- B. These reports will be reviewed by the IRB Chairperson or his/her designee and placed in the permanent IRB file and reviewed by the Chairperson or his/her designee with the next Continuing Renewal Request.
- C. If IND Safety Reports significantly alter the risk/benefit ratio to the subjects, the IRB may request revisions to the informed consent or suspend or terminate the protocol.

XXIV. EMERGENCY USE OF INVESTIGATIONAL DRUGS/DEVICES

- A. "Emergency Use", as defined by the FDA, means the 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 not sufficient time to obtain IRB approval. The investigator is still required to obtain informed consent under these circumstances.
- B. FDA exempts from IRB review the emergency use of a test article so long as the emergency use is reported to the IRB within five (5) working days of its occurrence. Any subsequent use of the test article is subject to IRB review. Subsequent use means any use of the test article that occurs after its initial emergency use.
- C. Although FDA regulation (21CFR 56.104) is designed to permit only a single emergency use for the treatment of one patient by one physician within an institution, the regulation is not intended to limit the authority of a physician to provide emergency care in a life-threatening situation. Should a second patient

require emergency use of the test article, either by the same or a second physician, the investigator must obtain approval from the FDA and/or sponsor. If it is probable that similar emergencies will require subsequent use of the test article every effort should be made either to sign on to the sponsor's protocol or develop a protocol for future emergency use. Either of these protocols would require IRB approval.

- D. The investigator, not the IRB, is responsible for contacting the FDA to obtain the test article.

XXV. INVESTIGATIONAL DRUG USE IN PATIENT ENTERING A SECOND INSTITUTION

- A. If a subject participating in a research project is admitted to a second institution for treatment of a condition unrelated to the research:
 - 1. Procedures should be in place for rapidly identifying test drugs and/or investigational devices (e.g. emergency contact number, investigator(s) names and un-blinding procedures)
 - 2. Local or treating physician determines that it is appropriate to continue the subject on the test drug, or, continue use of the investigational device.
 - 3. The investigator provides the treating physician with a copy of the signed informed consent, a list of potential side effects of the investigational drug or device and/or any other information the treating physician may need to insure the safety of the patient.
 - 4. The treating physician and/or institution where the subject is hospitalized may require a copy of the investigator's IRB Approval Notice.
 - 5. The investigator shall contact the pharmacy to arrange providing the treating physician with the test drug. The pharmacy will follow their department policy for procedures of dealing with drugs prescribed out-of-facility.
 - 6. The investigator remains responsible for test drug administration and follow-up.
 - 7. The investigator may need to report the event as an unexpected adverse incident, if the subject's hospitalization is possibly related to use of the test article.
 - 8. The investigator's IRB remains the IRB of record.

XXVI. Requirements for new equipment or device.

- A. Any protocol which necessitates the use of new equipment or a device that uses an energy source (e.g., electrical, gas tanks) will not receive final approval until the IRB has received a copy (or email) of the Clinical Engineering Approval Letter.



- B. The ninety day (90) deadline for an investigator response does not apply in the case of Clinical Engineering approval. If the only pending portion of a protocol is the delivery of equipment and approval of Clinical Engineering, the protocol can remain in the pending category until such time that the equipment is delivered and approved by Clinical Engineering.



**Attachment A
Categories of Research That May Be Reviewed by the
Institutional Review Board (IRB) Through an
Expedited Review Procedure¹**

Applicability

- (A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- (B) The categories in this list apply regardless of the age of the subjects, except as noted.
- (C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- (D) The expedited review procedure may not be used for classified research involving human subjects.
- (E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.
- (F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories

- 1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
 - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
 - (b) from other adults and children², considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

¹An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

²Children are defined in the HHS regulations as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.” 45 CFR 46.402(a)



3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, blood composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. [45 CFR 46.101\(b\)\(4\)](#). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects [45 CFR 46.101\(b\)\(2\)](#) and [\(b\) 3](#). This listing refers only to research that is not exempt.)
8. Continuing review of research previously approved by the convened IRB as follows:
 - (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
 - (b) where no subjects have been enrolled and no additional risks have been identified; or
 - (c) where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.



**ATTACHMENT B
EXEMPT CATEGORY DEFINED BY DHHS**

**CHILDREN'S HEALTHCARE OF ATLANTA INSTITUTIONAL REVIEW BOARD
HAS DETERMINED THAT THIS CATEGORY OF RESEARCH WILL NOT BE EXEMPT FROM
REVIEW BUT SHALL RECEIVE EXPEDITED REVIEW**

Currently, the Federal human subjects protection regulations (45 CFR 46.101(b) define the following six types of human subjects research as exempt:

- 1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- 2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), *survey procedures, interview procedures or observation of public behavior, unless: (does not apply to children 45CFR46:Subpart D401:b)*
 - (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- 3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
 - (i) the human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- 4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- 5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
 - (i) Public benefit or service programs;
 - (ii) procedures for obtaining benefits or services under those programs;
 - (iii) possible changes in or alternatives to those programs or procedures; or
 - (iv) possible changes in methods or levels of payment for benefits or services under those programs.
- 6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.



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Policy Number:	1.40	Original Date Issued:	April 26, 2002
Section:	Operations	Date Reviewed:	January 31, 2006
Title:	Research Contracting	Date Revised:	January 31, 2006
Regulatory Agency:			

I. POLICY:

- A. All contracts initiated for research purposes should be sent to the Director of the Research Department, Office of Grant Accounting and Contracts for approval and processing.

II. PROCEDURE:

- A. The Research department will assume the following responsibilities related to research contracts:
- Initial contract review
 - Obtaining review and feedback from Legal Services
 - Negotiating with the sponsoring agency
 - Obtaining the Senior Vice President for Medical Affairs' signature on the final copy
 - Forwarding the signed contract to the sponsoring agency
 - Returning the original executed contract to Legal Services
 - Distributing copies of the executed contract to:
 - Principal Investigator
 - Research department
 - Vice president/Director/Manager as requested



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 - Research department
 - Vice president/Director/Manager as requested



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Policy Number:	1.41	Original Date Issued:	April 26, 2002
Section:	Operations	Date Reviewed:	January 31, 2006
Title:	Patient Care Budgeting for Sponsored Research	Date Revised:	January 31, 2006
Regulatory Agency:			

I. POLICY:

All research procedure/diagnostic charges for Children's Healthcare of Atlanta will be based on fully-absorbed costs and will be determined by the Research department. The Research Director must approve all charges.

Professional service fees provided by non-employed Children's physicians shall be determined by the appropriate administrative office within the physician's department or private practice and must not exceed reasonable and customary fees.

The Research Department shall reject projects which include excessive professional, diagnostic or administrative fees.

II. PROCEDURE:

- A.** Research charge rates will be determined based upon current hospital charges, cost and reimbursement patterns at Children's Healthcare of Atlanta.
- B.** The Office of Grant Accounting and Contracts will work collaboratively with the Reimbursement Department using the relevant information related to charges to establish parameters for research charges.
- C.** Research charge rates will be reviewed at least annually.
- D.** The Office of Grant Accounting and Contracts will receive a current charge master for reimbursement bi-annually to be used as the basis for charges.
- E.** Once the Office of Grant Accounting and Contracts has set charges for a specific grant budget, the charges will not change during the life of the grant.



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Policy Number:	1.51	Original Date Issued:	January 24, 2006
Section:	Operations		
Title:	Intellectual Property Policy	Date Revised:	
Regulatory Agency:			

I. POLICY SUMMARY:

Children's Healthcare of Atlanta has established an Intellectual Property Policy to support research and development of commercially valuable works.

The policy is intended to encourage, support, reward and recognize the rights and interests of the contributors and the sponsor(s).

Children's will own all copyrightable, patentable, registered or other Intellectual Property created or developed by Children's personnel if the Intellectual Property is related to Children's personnel normal duties or is created or discovered with the use of Children's resources or support.

This policy will apply to Children's personnel who may receive Children's support, visitors with assigned duties at Children's or others who receive support from Children's, and students. Non-employees will own the Intellectual Property they create except where Intellectual Property is (1) work-for-hire (2) supported by direct allocation of funds through Children's for a specific project (3) commissioned by Children's (4) made with significant use of Children's support or personnel or (5) subject to contractual obligations.

Within the policy is a Distribution of Cumulative Net Revenue section to provide guidelines to be followed in distributing the Cumulative Net Revenue.

II. PREAMBLE TO CHILDREN'S HEALTHCARE OF ATLANTA INTELLECTUAL PROPERTY POLICY

Children's Healthcare of Atlanta's mission embraces three means to achieve our defining purpose. We strive to enhance the lives of children through excellence in patient care, research and education.

To support this mission and the commitment to use research and education to enhance the lives of children, Children's has established this Intellectual Property Policy and these procedures.



Although Children's does not undertake research or developmental work principally for the purpose of developing patents and commercial applications, patentable inventions and/or other valuable works sometimes result from the activities carried out wholly or in part with Children's funds and facilities. This policy is intended to encourage, support, reward and recognize the rights and interests of the contributors, the public and the sponsor(s).

In establishing this policy, Children's recognizes employees pursue areas of study and concentration, share the results of their intellectual efforts with colleagues and students and retain the traditional academic freedoms for the conduct of scholarly and scientific work. In addition, it is intended that application of this policy will take into consideration principles of open and full disclosure, overall equity, fairness to the contributors and Children's, and the need for understanding and goodwill among the parties who have an interest in Intellectual Property.

III. Ownership of Intellectual Property

Children's will own all copyrightable, patentable, registered, claimed or other Intellectual Property created or developed by Children's personnel if the Intellectual Property either (a) is related to the Children's personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise, or (b) was made with the use of Children's resources or support ("Children's Support").

A. Copyrightable Works. In keeping with tradition, Children's does not assert its rights in academic or scholarly Copyrightable Works, such as books, articles, and creations, including Works-for-Hire, except under circumstances in which the Copyrightable Works are either (a) related to Children's personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise, or (b) made with the use of Children's Support, and were:

- Specifically assigned and funded by Children's;
- Developed with the use of substantially more Children's Support than is normally provided to Children's personnel; or
- Developed under an externally funded agreement with Children's, unless otherwise provided in the agreement.

If there is any question as to whether a Copyrightable Work falls within the category of exempt Copyrightable Works, a determination will be made by the appropriate Vice President who shall have consulted with the Office of General Counsel ("OGC"). If the Vice President is unable to make a determination, or if the Children's personnel wishes to appeal the determination, the issue will be presented to the appropriate Senior Vice President who will finalize the decision with the Senior Leadership Team. After receiving



the advice of the General Counsel, the Senior Leadership Team will make the final decision.

- B. New Media. Ownership rights and control of the content included in New Media are governed by copyright and patent law and the provisions of this policy regarding Copyrightable Works. Subject to this Policy, Children's will assert ownership in New Media works under circumstances in which the content included in New Media (a) is related to the Children's personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise, or (b) was made with the use of Children's Support, and was:
- Specifically assigned and funded by Children's;
 - Developed with the use of substantially more Children's Support than is normally provided to Children's personnel; or
 - Developed under an externally funded agreement with Children's, unless otherwise provided in the agreement.

If there is any question as to whether a New Media work falls within the category of exempt Copyrightable Works, a determination will be made following the procedure set out in Section III.A.

- C. Patentable and Other Intellectual Property. Children's will assert ownership rights to patentable and other Intellectual Property not covered by No. III.A or III.B. which (a) is related to the Children's Personnel's normal duties (including clinical duties), course of studies, field of research or scholarly expertise, or (b) was made with the use of Children's Support, and was:
- Specifically assigned and funded by Children's;
 - Developed in whole or in part using Children's Support, including grants to Children's from external sponsors; or
 - Developed under an externally funded agreement with Children's, unless otherwise provided in the agreement.
- D. Trademarks and Service Marks. Children's will assert ownership rights to all related Trademarks and Service Marks in all circumstances. This applies to both common law claimed marks and registered marks.

IV. Obligations of Children's Personnel (Including Visitors and Students)

- A. Children's Personnel. All Children's Personnel must agree in writing to be bound by this Policy. Children's personnel who may receive Children's Support will sign an Intellectual Property Rights Agreement Form (the IP Rights Agreement, Exhibit A), to be filed in the following locations:



- Original to be retained by signatory;
- Original to be retained by the Department Vice President;
- Original to be retained in the laboratory/department files;
- Original to the relevant Supervisor; and
- Copy to the OGC.

The responsibility for ensuring that Children's personnel sign an IP Rights Agreement is allocated as follows:

- Children's Human Resources will be responsible for obtaining the signatures of Children's personnel, excluding visitors and students; and
- The Vice President will be responsible for obtaining the signature of each employee in the Department.

Children's personnel are bound by this policy regardless of whether they have signed an IP Rights Agreement.

- A. Visitors. Children's personnel will ensure that a visitor who has either (1) assigned duties at Children's or (2) receives Children's Support has signed a Visitor's Intellectual Property Agreement, (Exhibit B) available from the OGC. Visitors are obligated to adhere to the provisions of this policy regardless of whether they have signed a Visitor's Intellectual Property Agreement.
- B. Students. Children's generally does not claim ownership of Intellectual Property created by students in the course of their education. Student Contributors will own the Intellectual Property they create, except where the Intellectual Property:
- Is a Work-for-Hire;
 - Is supported by a direct allocation of funds through Children's for a specific project;
 - Is commissioned by Children's;
 - Makes significant use of Children's Support or personnel; or
 - Is otherwise subject to contractual obligations.

Students will promptly disclose to the OGC the existence of any Intellectual Property to which they have contributed (that is, Intellectual Property to which Children's may assert ownership rights pursuant to Section III).

Externally funded research may be subject to an agreement that imposes certain restrictions upon Children's and/or Children's personnel regarding Intellectual Property rights and confidentiality. If a student wishes to participate in Children's research under an agreement that imposes restrictions on Intellectual Property rights or confidentiality, an employee or the student will make a written request to the appropriate Vice President who, after consulting with the Office of General Counsel,



may grant permission, in writing, for the student to participate in that research. For good cause shown, the appropriate Vice President may also, after consulting with the Office of General Counsel, grant permission for a student to enter into agreements that bind the individual(s), but not Children's. However, Students may not engage in research leading to a thesis or dissertation under an agreement that imposes such restrictions regarding Intellectual Property rights and confidentiality.

V. Disclosure of Intellectual Property to the Office of General Counsel

Children's Personnel will promptly disclose the existence of any Intellectual Property (that is, Intellectual Property to which Children's may assert ownership rights pursuant to Section III) to the OGC. Delay in contacting the OGC may compromise the ability to secure effective legal protection for Intellectual Property. Publication or presentation of research results prior to filing a patent application may substantially compromise patent protection both in the United States and in foreign countries. Prompt disclosure is also necessary to ensure that the appropriate research sponsor is notified in a timely manner and that Children's is in compliance with the federal laws governing research or regulating the sponsor.

The Children's Intellectual Property Disclosure Statement Form (Exhibit C) is available from the OGC. Children's Personnel are encouraged to contact the OGC staff with questions.

The OGC will review all disclosures, obtain a preliminary determination as to the patentability and marketability of the Technology, and notify the Children's Personnel of its decision as soon as is reasonably possible.

VI. Release or Assignment of Certain Intellectual Property

At the time of disclosure of Intellectual Property (that is, Intellectual Property to which Children's may assert ownership rights pursuant to Sections III) to the OGC, or at any time thereafter, Children's Personnel may petition Children's to release or assign ownership of the Intellectual Property by completing a Petition for Release or Assignment (available from the OGC), obtaining approval from his/her Supervisors and submitting the form to the OGC, which office will submit the form with its recommendation to Children's Senior Leadership for final approval. An approved petition is required when Children's Personnel intend to pursue commercial development of Intellectual Property independently. Circumstances may exist where Children's is not interested in pursuing the commercialization of the Intellectual Property, and that determination will be made by the Senior Leadership. Petitions will be processed as soon as is reasonably possible, which shall mean not more than 120 days from the completion of the submission.



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Under all circumstances, Children's will retain a non-exclusive, royalty-free, perpetual license to use any released or assigned Intellectual Property for research, clinical service, and educational purposes.



VII. Distribution of Cumulative Net Revenue

It is anticipated that certain Children's Intellectual Property will generate revenue in various forms, including, but not limited to royalties or Equity. This section provides the guidelines to be followed in distributing the Cumulative Net Revenue derived from this Intellectual Property.

The Cumulative Net Revenue allocated to Children's pursuant to a licensed Technology or Copyrighted Work will be distributed by Children's in accordance with Table 1 "Distribution of Cumulative Net Revenue." Such distribution will take place not less than quarterly, unless otherwise agreed upon. Revenues generated from Children's Intellectual Property disclosed on or prior to the date on which this policy is adopted by Children's will be distributed as provided in this policy. Children's Personnel are not entitled to receive interest on sums deposited into or held by Children's.

**Table 1
Distribution of Cumulative Net Revenue**

	Gross Revenue up to \$25,000	Net Revenue up to \$4 million	Net Revenue \$4 million and over
Contributor Share	100%	33%	25%
Program Share	0%	33%	33%
General Children's Share	0%	34%	42%

- A. Contributor Share. Contributors to Children's Intellectual Property that generates Cumulative Net Revenue are entitled to receive one hundred percent (100%) of the first \$25,000.00 in Gross Revenue, and thereafter a portion of Cumulative Net Revenue. Children's Personnel receiving Contributor Share funds will be responsible for any personal tax obligations that may arise. Children's will assume that all contributors contributed equally to the development of Intellectual Property, unless contributors request a different allocation. To be effective, such a request must be made by all contributors in writing to OGC and signed by all contributors. Contributors shall have the right to designate other individuals who participated in the design and/or development by submitting the designation in writing to the OGC. If any dispute arises as to the allocation of contributors Share among multiple Contributors, or as to whether a Children's personnel is a contributor, the dispute will be resolved as set forth in Section X., Conflict Resolution.

Contributors will be entitled to receive their Contributor Share funds if they leave the employment of Children's. The estate or designated beneficiaries of a deceased contributor will be entitled to receive his/her contributor share funds. In the event of any dispute or delay arising in the course of probating the estate of a contributor,



Children's will be entitled to retain the Contributor Share in an escrow account until the dispute or delay is resolved.

- B. Program Share. Use of funds in this account will be subject to the policies established by the Program and must be used in the program.
- C. General Children's Share. A portion of the Cumulative Net Revenue generated by Children's Intellectual Property will be allocated to a General Children's account. Distribution of these funds will be done upon the review and approval of the SVP and COO. Use of these funds must be for research purposes.

VIII. Distribution of Equity

- A. Contributor Equity. It is anticipated that certain Children's Intellectual Property will generate revenue in the form of equity. This section provides the guidelines for the distribution of any equity that Children's receives in the exchange for the grant of rights to Children's Intellectual Property. Contributors will be allowed to receive such Equity subject to and consistent with the following policies:
 - This IP Policy;
 - Children's Conflict of Interest (Standards of Conduct) Policies
 - Children's Conflict of Interest Policy with Respect to Vendors

All arrangements for the receipt of equity by contributors must be approved in advance by the OGC and Senior Leadership.

- B. Children's Equity. Equity received by Children's will be distributed according to the distribution formula set forth in Table 1, column 2 ("Net Revenue up to \$4 million") either from Children's promptly upon receipt from the Commercial Venture, or directly from the Commercial Venture.

IX. Intellectual Property Developed with External Funding

Notwithstanding any other provisions of this Policy, all compensation received by Children's, resulting from Children's Intellectual Property developed in whole or in part with funds received from a source outside Children's will be used in compliance with any terms or conditions imposed by the granting agency or source.

X. Intellectual Property Developed by Third Parties with Children's Funding

The funding of outside research by Children's shall be only pursuant to written agreement providing for terms that return to Children's an appropriate return on the funding. The distribution of Cumulative Net Revenue and distribution of equity shall be generally in line with the provisions of this policy. Exceptions may be made in consultation with the OGC.



XI. Conflict Resolution

Unless otherwise provided in this Policy, any disputes that arise will be resolved by Leadership in consultation with the OGC, relevant supervisors and other appropriate parties.

XII. Use of Children's Name, Logo or Trademarks/Service Marks

Use of Children's name, logo or marks in any commercial setting requires prior written approval from Children's. Requests for such approval should be submitted to the Marketing Department, and a decision will be made in conjunction with the OGC.

Forms: [maintained in OGC]

- A. Intellectual Property Rights Agreement
- B. Visitors Intellectual Property Rights Agreement
- C. Intellectual Property Disclosure Statement
- D. Petition for Release or Assignment



APPENDIX A

Definition of Terms

For the purposes of this Intellectual Property Policy, the following terms will have the following meanings:

Author shall mean any individual who has participated in the creation of a work that may be protected under United States copyright law, 17 U.S.C. §102.

Commercial Venture shall mean any legal entity that has licensed or intends to license Children's Intellectual Property for further development or commercialization.

Commercialization Costs shall mean all payments made to third parties for the following costs and expenses:

- Actual expenses incurred by Children's in protecting, developing or marketing any Children's Intellectual Property;
- Actual expenses associated with negotiations in connection with licensing any Children's Intellectual Property; or
- Contractual obligations associated with any Children's Intellectual Property, such as distributing revenues to joint inventors who are not Children's personnel.

Contributor shall mean any individual(s) who is an Inventor and/or an Author with respect to a specific Intellectual Property, whether or not that Intellectual Property is protected under the patent and copyright laws of the United States.

Copyrightable Work(s) shall mean an original work of authorship fixed in a tangible medium of expression, as described in the Copyright Act, 17 U.S.C. §102, such as, but not limited to, books, articles, lectures, musical compositions, films, charts and other visual aids, software, video/audio tapes, and video/audio broadcasts.

Children's Intellectual Property shall mean Intellectual Property that is either owned by or assignable, in whole or in part, to Children's or its assignee or designee, as provided in this Policy.

Children's personnel shall mean all persons working at Children's, including but not limited to:

- Employees, whether full-time, part-time, or PRN;
- Outside consultants or contractors; and
- Post-graduate students who are enrolled in any Children's program; and



- Members of the Professional Staff with a contract with Children's.

For purposes of this Policy, Children's personnel also includes any of the above associated with any Children's Affiliate.

Children's Support shall mean any resources of Children's received or used by Children's personnel, including but not limited to monies from internal or external sources, facilities, space, equipment, services or personnel.

Intellectual Property shall include, but not be limited to, inventions (whether patentable or not), Copyrightable Works, Trademarks, Service Marks, domain names, trade secrets, trade dress rights, formulas, designs, software, programming code, new media, intangible rights in machines, compositions of matter and devices, techniques, processes, procedures, systems or formulations and any other intellectual property rights existing under International, Federal or State law.

Intellectual Property Disclosure Statement Form shall mean the form supplied by the OGC and submitted by a Children's personnel to the OGC for the purpose of disclosing an Intellectual Property. The form is available from the OGC.

Inventor shall mean any Children's personnel who is an inventor under applicable United States law of a new and useful process, machine or composition of matter, or any new and useful improvement thereof, whether patentable or not. Inventorship shall be determined by outside counsel to Children's.

IP Agreement Form or Intellectual Property Rights Agreement Form shall mean the form submitted by a Children's personnel who shall receive or may have opportunities to receive direct Children's support. The form is available from the OGC.

New Media shall mean digital or electronic media, including but not limited to software, video/audio tapes, CD-ROM, DVD-ROM, Internet-based media, and other multimedia materials that are used for the purpose of education or the dissemination of knowledge, but does not include technology that may be embodied in the new media.

OGC shall mean the Office of General Counsel at Children's. (Note: Print forms from this site).

Patent shall mean a legal grant made by the United States government pursuant to 35 U.S.C. §101, et. seq., for certain inventions or discoveries that constitute any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, or a similar grant made by any other government pursuant to the laws of that country.

Software shall mean one or more computer programs and any associated operational procedures, manuals or other documentation, whether or not it may be protected under United States patent or copyright law.



Students shall mean individuals enrolled at an accredited institution.

Supervisor shall mean the Director, Department Head, Vice President and/or other individual having direct supervisory authority or responsibility over a Children's personnel.

Technology shall mean the tangible and intangible results of research and scholarship and related Intellectual Property rights, whether or not patentable or copyrightable, but excluding Copyrightable Works as defined above. Technology may include, but is not limited to:

- Prototype devices;
- Novel biological materials;
- New chemical compounds;
- Materials having novel optical or electronic characteristics; and
- Software and programming code, where software is not excluded as a Copyrighted Work.

Trademark shall mean a word, name, symbol, device or a combination of these used to identify the source or sponsor of a product. Similarly, **Service Mark** shall mean a word, name, symbol device or a combination of these used to identify the source or sponsor of a service.

Visitors shall be considered Children's Personnel for the purposes of this Policy, except that they will be required to sign a Visitor's Intellectual Property Agreement Form.

Visitor's Intellectual Property Agreement Form shall mean the form to be signed by Visitors who either:

- Have assigned duties and responsibilities at Children's; or
- Utilize Children's Support in the development or creation of Intellectual Property.

Work for Hire shall mean "Work Made for Hire" as defined under the Copyright Act, 17 U.S.C. §101, which refers to "(1) a work prepared by an employee within the scope of his or her employment" and certain specially ordered or commissioned works.



Administrative and Operational Policies and Procedures

Policy Number:	1.52	Original Date Issued:	January 31, 2006
Section:	Operations	Date Reviewed:	
Title:	Sponsored Research Budgets	Date Revised:	
Regulatory Agency:			

I. POLICY:

The budget for sponsored research occurring within Children's Healthcare of Atlanta must be developed in collaboration with the research department and approved by the Office of Grant Accounting and Contracts. Expenses applied to sponsored research studies will be managed by the Department of Research in collaboration with the Principle Investigator and Corporate Finance.

II. PROCEDURE:

A. Budget Development and Approval – Pre-Award

1. Children's Primary Awardee
 - a. Includes all direct and indirect costs incurred by Children's
 - b. Includes all direct and indirect costs incurred by a non-Children's entity (i.e. Emory, GA. Tech, private MD)
 - c. Children's will initiate a subcontract with the non-Children's entity
2. Non-Children's Primary Awardee
 - a. All Children's direct and indirect costs are included in subcontract between Children's and the non-Children's entity (Primary Awardee).
3. All budgets must be approved in writing by the Children's Research Department Office of Grant Accounting and Contracts prior to submission to either the non-Children's entity or funding agency.

B. Post-Award Grant Management

1. Children's Primary Awardee
 - a. Subcontractors shall mail invoices for work performed to the Clinical Research Department, Office of Grant Accounting and Contracts.
 - b. Office of Grant Accounting and Contracts shall obtain written approval of the invoice from the Principal Investigator (PI). By approving the invoice, the PI is certifying that the work was performed and does not exceed the amount budgeted for such work.



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- c. The Office of Grant Accounting and Contracts will review the invoice for compliance with the approved budget and process the invoice to Corporate Finance for payment to the subcontractor.
 - d. All other direct expenses allowed in the approved budget incurred by Children's and/or the personnel listed on the award shall be expensed directly to the grant account number assigned by Children's. All expenses should be approved by the PI and submitted to the Clinical Research Department, Office of Grant Accounting and Contracts for final approval and processing to Corporate Finance.
 - e. Monthly Financial Responsibility reports and Monthly Transaction reports will be provided to the Office of Grant Accounting and Contracts who will review for accuracy and provide a copy of reports to the PI.
 - f. The Office of Grant Accounting and Contracts will work in partnership with Corporate Finance to insure that federal funds are electronically drawn down from the Funding Agency in accordance with the federally approved direct cost budget and the federally approved Indirect Cost Agreement and applied to the correct accounts and offset already incurred budgeted expenses.
 - g. The Office of Grant Accounting and Contracts will work in collaboration with PI, Research Coordinator or appropriate finance administrator/business manager to insure that non-federal funds are paid by sponsor.
2. Non-Children's Primary Awardee
- a. Children's establishes a grant account number
 - b. Direct expenses incurred by Children's are charged to grant account
 - c. Office of Grant Accounting and Contracts works with study coordinator to invoice non-Children's entity for expenses incurred by Children's
 - d. Payments from non-Children's entity are received by Office of Grant Accounting and Contracts and deposited to grant account
 - e. Monthly Financial Responsibility reports and Monthly Transaction reports will be provided to the Office of Grant Accounting and Contracts.



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Policy Number:	1.53	Original Date Issued:	January 31, 2006
Section:	Operations	Date Reviewed:	September 5, 2007
Title:	Time and Effort Reporting for Federally Funded Grants	Date Revised:	September 5, 2007
Regulatory Agency:			

I. POLICY:

All Children's Healthcare of Atlanta employees and outside contractors, involved in grants (awards), are required to report time and effort for federally funded projects, following the guidelines of Office of Management and Budget (OMB) Circular A122.

Definitions:

Effort Reporting: A means of verifying that appropriate salary and wage expenses were charged to sponsored accounts. Time devoted by the individual to any activity, stated as a percentage.

II. PROCEDURE:

- A. Effort is not calculated on a 40-hour workweek. If an individual works 80 hours in a week, 40 hours represents 50% effort.
- B. Contractors Effort Reporting: On a monthly basis the contractor will submit the Physician Contract Service Hours Documentation Form (see example, Attachment A) to the Office of Grant Accounting and Contracts. This document reflects the contracted percent effort on grants and certifies the actual percent effort performed. Upon receipt of documentation payment will be paid per the grant budget
- C. Children's Employees Effort Reporting: The Time and Effort Certification Form (Attachment B) reflects the distribution of activity of each employee and will be maintained for all staff members (professionals and nonprofessionals) whose compensation is charged, in whole or in part, directly to awards.
 1. The Time and Effort Certification Form will reflect an after-the-fact determination of the actual activity of each employee. Budget estimates (i.e., estimates determined before the services are performed) do not qualify as support for charges to awards.
 2. Each Time and Effort Certification Form will account for the total activity for which employees are compensated and which is required in fulfillment of their obligations to the organization.



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3. The Time and Effort Certification Forms can be obtained from Careforce/Clinical Research/Office of Grants Accounting and Contracts/Forms and are to be completed by the employee certifying the contracted effort.
4. If the percent effort differs from the contracted amount listed, please contact the Officer of Grants Accounting and Contracts in the Research Department at Children's Healthcare of Atlanta.
5. Individuals may be criminally prosecuted under the False Claims Act for making incorrect or false statements on an effort certification.
6. Time and Effort Certification Forms will be kept for 3 years from the closeout of the project

**Attachment A
(Sample)**

PHYSICIAN CONTRACT SERVICE HOURS DOCUMENTATION

Position/Agreement: _____

Physician(s) Providing Services: _____

Month/Year Services Provided: _____

It is the policy of Children’s Healthcare of Atlanta, Inc. and its affiliates, (“Children’s”) to comply with all applicable federal, state, and local laws and regulations, both civil and criminal, as well as those pertaining to tax exempt status. Accordingly, in its agreements with physicians, compensation for physician services will be set in advance, and will be reasonable and reflect fair market value. Compensation or remuneration available to the physician pursuant to an agreement shall not vary based on the volume or value of services referred or generated by the physician.

To ensure that compensation paid to you pursuant to your Agreement is consistent with fair market value for services provided and will not constitute impermissible remuneration, please indicate below the percent effort of service provided per month.

Please note that hours indicated should reflect only those hours during which services were provided pursuant to this Agreement; therefore, hours for which professional fees are billed should not be included.

Please note that pursuant to this Agreement you must maintain books, documents, or records to verify the hours worked and services provided. If your percent effort differs from the contracted amount listed below, please contact the Office of Grant Accounting and Contracts in the Research Department at Children's Healthcare of Atlanta.

- | | | |
|---------------|--|------------|
| 1. | % Effort for Principal Investigator Grant: | _____ |
| 2. | % Effort | _____ |
| 3. | % Effort | _____ |
| 4. | % Effort | _____ |
| Total Effort: | | _____ 100% |

Physician Signature

Date

Administrative Approval

Date

**Attachment B
(Sample)**

**CHILDREN'S HEALTHCARE OF ATLANTA
TIME AND EFFORT CERTIFICATION FORM**

Employee Name

Employee ID#

Job Title

Department

Account
% Effort
05588
AHRQ Grant

Account
%Effort

Account
%Effort

Account
%Effort

Q1
Q2
Q3
Q4

I certify that this report represents a reasonable estimate of the effort I expended during this time period.

Employee Signature

Printed Name

Date



Administrative and Operational Policies and Procedures

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Policy Number:	1.55	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	
Title:	Investigational Drugs, Biologics, and Dietary Supplements in Research	Date Revised:	
Regulatory Agency:			

I. POLICY:

Research at Children Healthcare of Atlanta that involves the investigational use of drugs, biologics, and dietary supplements must conform to Food and Drug Administration (FDA) regulations.

The purpose of this policy is to describe the various mechanisms for obtaining, testing, and using drug and biologic products in compliance with federal regulations.

Definitions:

Biological Product: A virus, therapeutic serum, toxin, antitoxin, vaccine, blood product, blood component or derivative, allergenic product, or analogous product or applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Clinical Investigation: Any experiment that involves a test article and one or more human subjects. The terms research, clinical research, clinical trial, clinical study, study, and clinical investigation are often used.

Investigational New Drug (IND): A new drug, antibiotic, or biological product that is used in a clinical investigation.

II. PROCEDURE:

A. Investigational New Drug (IND) Exemption

Federal law prohibits the distribution of a new drug or biologic until the FDA reviews the clinical data and determines that the product is safe to use and is effective for a specified indication.

Investigators/sponsors who wish to test a new product must acquire an exemption before any testing may begin. Complete IND information must be submitted with any protocol submitted to the IRB that involves an investigational drug or biologic. Investigators are required to submit IND information provided by the sponsor, or if



the investigator is also the sponsor a copy of the letter from the FDA that assigns the IND. This will be required as part of the protocol application. The IRB will not release a final approval until all IND information is complete.

Protocol administrators will be responsible for making sure this information is obtained prior to release of the approval notification and informed consent document. If there is any question as to whether an IND is required, the IRB may require, as part of the review and approval process, that the investigator contact the FDA to discuss the protocol and to determine if an IND is required. Investigators who propose to use investigational or marketed drugs for unapproved indications must also follow FDA regulations 21 CFR 50, 56 and 312.

For the most part, the FDA regulations are the same as DHHS regulations 45 CFR 46. The regulations are the same with regard to IRB organization, composition, procedure, record keeping, and criteria for approval of research protocol and informed consent documentation. There are additional determinations that must be considered for protocols that involve the use of investigational products.

1. For all investigations subject to IND regulations, the investigator is required to be knowledgeable about the requirements of FDA regulations and must be listed on a 1572 Form in order to administer an investigational product.
2. When it is determined that an IND is required, the research will not be approved until the IND information is submitted to the IRB. At the time of continuing review the IRB may request additional documentation to be certain the investigator is following the IND requirements. If the investigator holds the IND, a copy of the annual report to the FDA may be requested.

B. Use of a Marketed Drug or Biologic in a Manner for Which it is not Approved

1. Off Label Use

When the FDA approves a drug or biologic it also includes the indications for which it is approved. Variance from the intended use is referred to as "off label use." Good medical practice and patient interest require that physicians use commercially available drugs and biologics in a knowledgeable way and with sound judgment.

If a physician uses a product for an indication that is not in the approved labeling, he or she has the responsibility to be well informed about the product, and to base its use on firm scientific rationale and sound medical evidence. Use of a product for an individual patient in this manner may be considered "medical practice" and does not require submission of an IND or a protocol to the IRB. This may be considered "off label use" and not research use.

2.

Investigational Use

The investigational use of a marketed drug or biologic involves the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test product is to develop information about the product's safety or efficacy, submission of a protocol to the IRB is required. This is usually performed as a protocol with a hypothesis for a group of defined patients. In this situation the intent is not solely to treat one patient but to look at a group of patients to answer a specific, predetermined set of questions. In addition, an IND will be required from the FDA.

An IND will not be required in the following situations if **all** conditions are met:

- a. The study is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in labeling.
- b. The study is not intended to support a significant change in the advertisement for the product.
- c. The study does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product.
- d. The study is conducted in compliance with the requirements for IRB review and informed consent.
- e. The study is conducted in compliance with the requirements for the promotion and sale of drugs.
- f. The study does not intend to invoke the requirements of 21 CFR 50.24 (exceptions from informed consent for emergency research).

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires submission to the FDA for an IND, the investigator is advised to contact the FDA directly to determine if this is required. The IRB may require that an investigator contact the FDA if this has not been done at the time of IRB review. If the FDA indicates that an IND is not required, documentation of contact with the FDA is required. This may be either a written notification from the FDA, or documentation of contact with the FDA, including who was contacted, the phone number, the time of the call, and a summary of the information provided by the FDA.

C. Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, test articles may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, a

life-threatening, or a debilitating condition, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects, or the thoroughness and scientific integrity of product development and marketing approval.

1. Open Label Protocol or Open Protocol IND

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued to enable the subjects and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review of the protocol and informed consent.

2. Treatment IND

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND [21 CFR 312.34 and 312.35] 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.

A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

- a. the drug is intended to treat a serious or immediately life-threatening disease;
- b. there is no satisfactory alternative treatment available;
- c. the drug is already under investigation, or trials have been completed; and
- d. the trial sponsor is actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent.

3. Parallel Track

The FDA's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

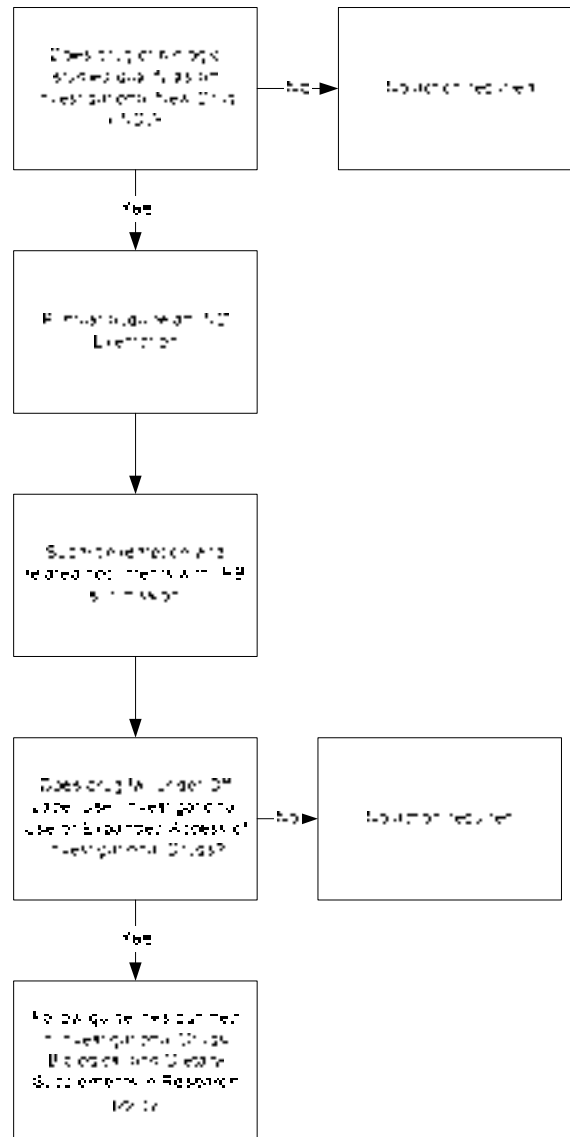


D. When a Patient is Hospitalized on an Investigational Drug from another Institution/Investigator

When this situation arises, investigators are urged to immediately call the IRB Office to discuss the specifics of the situation. The determination must be made as to whether the original principal investigator (PI) will continue to maintain responsibility for the patient on the research protocol, or whether this responsibility will be transferred to a physician at Children's. In the first case, as long as the follow-up and care of the patient remain the responsibility of an investigator at another institution, review and approval by the IRB is not usually required. In this situation, Children's and its investigators are not a participating research site. However, Children's physicians are to determine whether the patient signed an informed consent and the name of the physician responsible, and are to obtain any information necessary to safely continue use of the investigational drug (e.g., information about possible adverse events). It is also recommended that the PI be contacted so that he or she may be advised about the hospitalization of the patient, and to obtain any information about the investigational drug. If the care of a child on an investigational drug is being transferred to a Children's physician, this request must go through the IRB.

INVESTIGATIONAL NEW DRUG (IND) EXEMPTION

CHILDREN'S HEALTH CARE OF ATLANTA





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Policy Number:	1.56	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	
Title:	Investigational Devices	Date Revised:	
Regulatory Agency:	FDA		

I. **POLICY:**

Research that involves the use of investigational devices must conform to Food and Drug Administration (FDA). The FDA regulations for investigational devices are listed in 21 CFR 812; FDA informed consent and Institutional Review Board (IRB) regulations are listed in 21 CFR 50 and 56, respectively. The IRB will document in their minutes any determination that a device poses a significant risk or non significant risk device.

Definitions

Medical Device: In part, any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for *in vitro* diagnosis of disease and other medical conditions such as pregnancy.

Significant Risk (SR) Device: A device that presents a potential for serious risk to the health, safety, or welfare of a subject, and 1) is intended as an implant; 2) is used in supporting or sustaining human life; 3) is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (Appendix A)

Non-significant Risk (NSR) Device: A device that does not meet the definition of a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the IRB regulations. (Appendix B)

510(k): A device not yet approved by the FDA but determined by the FDA to be substantially equivalent to a device that was marketed prior to the passage of the Medical Device Amendments of 1976. Devices that qualify as 510(k) may be marketed immediately, without investigation of safety and efficacy. Research activities that involve a 510(k) do not require an IDE (see below) prior to approval



by the IRB; however, the IRB will require written documentation that a 510(k) has been granted. This is usually obtained from the sponsor.

Investigational Device Exemption (IDE): An exemption from certain regulations described in the medical device amendments that allows the shipment of an unapproved device for use in a clinical investigation. The sponsor of an SR device is required to apply to the FDA for an IDE before the clinical research may begin. There are abbreviated requirements for NSR devices that do not involve filing with the FDA.

Humanitarian Use Device (HUD): A HUD is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year.

Humanitarian Device Exemption (HDE): An HDE is an application that is similar to a permarket approval (PMA) application, but exempt from the effectiveness requirements of a PMA. An HDE authorizes marketing of a Humanitarian Use Device (HUD).

II. PROCEDURE:

- A. **Distinguishing the Difference Between SR and NSR Device Studies**: The consequences of the SR/NSR decision are very important. SR device studies are governed by the IDE regulations (21 CFR 812). NSR device studies are subject to fewer regulatory controls than SR studies, and are governed by the abbreviated requirements (21 CFR 812.2(b)).
- i. The major regulatory differences between the two concern the approval process, and record keeping and reporting requirements.
 - ii. The SR/NSR decision is also of consequence to the FDA because the IRB serves, in a sense, as the FDA's surrogate with respect to the review and approval of NSR studies.
 - iii. Sponsors are responsible for the initial assessment of an investigational device. If it is determined that a device presents significant risk, the sponsor must apply to the FDA.
 - iv. If an investigator or a sponsor proposes to the IRB to undertake an NSR investigation, the IRB must make a separate and independent determination that the study is, in fact, an NSR device study.
 - v. The IRB's determination that a device is an NSR device must be documented in the IRB's minutes.
 - vi. If the IRB believes that a study is an SR device study, the investigation may not begin until both the IRB and the FDA approve the study.
- B. **The NSR/SR Decision**: The assessment of whether or not a device study presents an NSR is initially made by the sponsor.



- i. If the sponsor identifies a study as an NSR, the sponsor is to provide the IRB with an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study.
 - ii. The sponsor is expected to provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information the IRB deems necessary to make its decision. The IRB may also request an opinion from the FDA.
 - iii. The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the initial assessment and approves the study, the study may begin without submission of an IDE application to the FDA. If the IRB disagrees, the sponsor is to notify the FDA that an SR determination has been made. The study may be conducted as an SR investigation following FDA approval of an IDE application.
 - iv. The risk determination will be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, the IRB will consider the nature of the harm that may result from use of the device.
 - v. Studies in which the potential harm to subjects may be life-threatening, may result in permanent impairment of a body function or permanent damage to body structure, or may necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure, are to be considered SR. Moreover, if the subject must undergo a procedure as part of the investigational study (e.g., surgical procedure), the IRB must consider the potential harm that may be caused by the procedure in addition to the potential harm that may be caused by the device.
 - vi. The FDA will make the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with an IRB decision to identify a study as an NSR device study, an IDE application must be submitted to the FDA. On the other hand, if a sponsor files an IDE with the FDA because it is presumed to be an SR study, but the FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study must be presented to the IRB as an NSR investigation.
- C. **IRB Responsibilities Following SR/NSR Determination:** If the IRB identifies the study as SR, the IRB will notify the investigator who will, in turn, notify the sponsor of the SR determination. An IDE will be obtained by the sponsor, and the IRB will review the protocol, applying the requisite criteria (21 CFR 56.111). If the IRB identifies the study as NSR, the IRB will proceed to review the study, applying the requisite criteria (21 CFR 56.111). If the study is approved by the IRB, the sponsor and the investigator must comply with abbreviated IDE requirements (21 CFR 812.2(b)), and informed consent and IRB regulations (21 CFR 50 and 56). The determination that a device is an NSR device must be documented in the IRB minutes.



- D. **The Decision to Approve or Disapprove a Study**: Once the SR/NSR decision is reached, the IRB is to consider whether or not the study should be approved. The criteria for deciding if SR and NSR studies should be approved are the same as those for any other study.
- i. If a device is classified as a significant risk device, the IRB will require written documentation from the sponsor which includes the IDE number.
 - ii. If the investigator also serves as the sponsor of a significant risk device, a copy of the letter from the FDA will be requested which assigns the IDE number. This information should be submitted as part of the protocol application and the protocol approval will not be released until the information is provided. Protocol administrators will be responsible for making sure this information is obtained prior to release of the approval notification and informed consent document.
 - iii. The IRB is to ensure that the risks to subjects are minimized, and are reasonable in relation to the anticipated benefits and knowledge to be gained; that subject selection is equitable, that informed consent materials and procedures are adequate; and that provisions for monitoring the study and protecting the privacy of subjects are acceptable. To ensure that the risks to subjects are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation are to be compared to the risks and benefits of alternative devices or procedures.
 - iv. The minutes of IRB meetings must document whether a device has been determined to be a significant risk or non-significant risk device and the rationale for SR/NSR decisions, as well as the subsequent approval or disapproval decisions regarding the clinical investigation.
 - v. Any protocol that is considered SR is to be reviewed by the full IRB. Generally, IRB review, at a convened meeting, is also required when NSR studies are reviewed because the IRB must agree that the study is an NSR device investigation.
 - vi. At the time of continuing review the IRB may request additional documentation to be certain the investigator is following the IDE requirements. If the investigator holds the IDE for a significant risk device, a copy of the annual report to the FDA may be requested.
- E. **Control of Investigational Devices**: Investigators are responsible for control of the investigational devices used in their studies. The actual control plan will depend upon the type of device, the number of units to be received at any one time, and the proposed use. The protocol application submitted to the IRB must include a description of the following:
- Location and manner of the receipt of the device
 - Location and manner of the secure storage of the device
 - Those who have access to the device and how access is controlled
 - How the device will be tracked when utilized in a patient
 - How extra units will be stored or returned to the manufacturer



- How device receipt, use, and return will be logged or otherwise documented

This plan will be reviewed as part of the protocol application by the IRB members. Any questions regarding control of devices will be resolved before final approval of the protocol is granted.

F. Summary of FDA Requirements for Investigators Who are Also Considered Sponsors of New Devices:

Major Responsibilities of Sponsors for Significant Risk Device Studies

1. Obtain FDA and IRB approval for IDE.	(21 CFR 812.42)
2. Select investigator(s) with appropriate training and experience.	(21 CFR 812.43)
3. Select monitor in accordance with FDA regulations.	(21 CFR 812.43)
4. Ship investigational devices only to qualified investigators.	(21 CFR 812.43)
5. Obtain a signed agreement from the investigator using the required FDA documents.	(21 CFR 812.43)
6. Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations.	(21 CFR 812.45)
7. Ensure that investigator(s) are complying with FDA, IRB, and sponsor requirements.	(21 CFR 812.46)
8. Conduct an evaluation of unanticipated adverse events and terminate the study if necessary.	(21 CFR 812.46)
9. Resume terminated studies only after receiving approval from the FDA and IRB.	(21 CFR 812.46)
10. Maintain accurate and complete records in accordance with FDA regulations.	(21 CFR 812.140)
11. Provide required reports to IRB, investigator(s), and FDA in a timely manner.	(21 CFR 812.150)
12. Label the device in accordance with FDA requirements.	(21 CFR 812.5)
13. Promote the device in accordance with IRB and FDA requirements.	(21 CFR 812.7)
14. Comply with federal regulations regarding emergency use.	(21 CFR 812.47)



Major Responsibilities of Sponsors with Non-significant Risk Device Studies

1. Label the device in accordance with FDA requirements.	21 CFR 812.5
2. Obtain IRB approval of the investigation as a non-significant risk device study and maintain IRB approval during the investigation.	21 CFR 812.2
3. Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver.	21 CFR 812.2
4. Comply with FDA requirements for monitoring the study. (See items 7-9, above, for monitoring requirements.)	21 CFR 812.46
5. Maintain accurate and complete records in accordance with FDA regulations, and report the results to the FDA, IRB, and investigators.	21 CFR 812.140 and 21 CFR 812.150
6. Ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties.	21 CFR 812.140 and 21 CFR 812.150
7. Promote the device in accordance with IRB and FDA requirements.	21 CFR 812.7

G. **Humanitarian Use Devices (HUD)**: HUDs must receive approval for use in marketing through the receipt of a **Humanitarian Device Exemption (HDE)**, which exempts the device from the standard clinical investigation requirements regarding effectiveness. A HUD covered under an HDE may be administered only after it is approved by the IRB. Unlike an IDE, which gives the sponsor approval to conduct a clinical investigation of the safety and effectiveness of a device, an HDE authorizes the marketing of a HUD for clinical Purposes in the absence of clinical data that demonstrate its effectiveness. The IRB plays a critical role in the HUD process by performing initial review and providing continued monitoring of the device.

- In reviewing the use of a HUD, the IRB applies all required FDA regulatory criteria.
- Because the use of a HUD does not constitute "research" or an "investigation," the FDA specifies that informed consent requirements need not be applied; however, the IRB may require that informed consent be obtained. At Children's, informed consent requirements are necessary. The consent is to describe the status of the device, the intended use, and all of the other required elements of an informed consent document.



- The IRB reviews and approves the general use of the device. A protocol application is to be submitted. The IRB acknowledges that some sections of the protocol application may not apply in this situation.
- The IRB may impose specific surveillance or reporting requirements on the use of a given HUD, in accordance with any criteria the IRB deems appropriate. Investigators will receive a continuing review notification and will be asked to follow the same procedures.

III. REFERENCES:

Children's Hospital Boston
21 CFR 812
21 CFR 50
21 CFR 56



Appendix A

Examples of Significant Risk Devices (not inclusive)	
General Medical Use	
Artificial skin and interactive wound and burn dressings. Catheters: Urology with anti-infective coatings; Surgical long-term subcutaneous, percutaneous, implanted, and intravascular; Neurological cerebrovascular, occlusion balloon; Cardiology transluminal coronary angioplasty, intra-aortic balloon.	Collagen implant material. Implantable craniofacial prostheses. Implantable, closed loop infusion pumps. Implantable vascular access devices. Repeat access devices for surgical procedures. Surgical lasers. Sutures.
Anesthesiology	
Breathing gas mixtures. Bronchial tubes. Electroanesthesia apparatus. Epidural and spinal catheters. Epidural and spinal needles. Esophageal obturators.	Gas machines for anesthesia and analgesia. High frequency jet ventilators. Rebreathing devices. Respiratory ventilators. Tracheal tubes.
Cardiovascular	
Aortic and mitral valvuloplasty catheters. Arterial embolization devices. Cardiac assist devices. Cardiac bypass devices, ECMO. Cardiac pacemaker/pulse generators. Cardiopulmonary resuscitation devices. Cardiovascular/intravascular filters. Coronary artery retroperfusion systems. Coronary occluders for PDA and ASD. Implantable cardioverters/defibrillators.	Laser coronary angioplasty devices. Myoplasty laser catheters. Organ storage/transport units. Pacing leads. Peripheral, coronary, pulmonary, renal vena caval, and peripheral vascular stents. Replacement heart valves. Ultrasonic angioplasty catheters. Vascular and arterial graft prostheses.
Dental	
Absorbable materials to aid in healing of periodontal defects. Bone morphogenic proteins with and without bone. Dental lasers for hard tissue applications.	Endo-osseous implants and associated bone filling/augmentation materials. Subperiosteal implants. Temporomandibular joint prostheses.



Appendix A (continued)

Examples of Significant Risk Devices (not inclusive), <i>continued</i>	
Ear, Nose, and Throat	
Auditory brainstem implants. Cochlear implants.	Laryngeal implants. Total ossicular prosthesis replacements.
Gastroenterology and Urology	
Anastomosis devices. Balloon dilation catheters. Biliary stents. Water treatment systems for hemodialysis, components. Dialysis delivery systems. Hemodialyzers and hemofilters.	Lithotripters. Peritoneal dialysis devices. Peritoneal shunt. Plasmapheresis systems. Urethral occlusion devices. Urethral Sphincter prostheses. Urological stents.
Neurological	
Electroconvulsive therapy devices. Hydrocephalus shunts. Implantable intracerebral/subcortical stimulators.	Implantable intracranial pressure monitors. Implantable spinal cord and nerve stimulators and electrodes.
Ophthalmics	
Class III ophthalmic lenses. Contact lens solutions intended for direct instillation in the eye using new agents. Corneal implants. Corneal storage media. Epikeratophakia lenticules.	Extended wear contact lenses. Eye valve implants for glaucoma. Intraocular lenses. Keratoprotheses. Retinal reattachment systems. Viscosurgical fluids.
Orthopedics and Restorative	
Bone growth stimulators. Calcium tri-phosphate hydroxyapatite ceramics.	Collagen and bone morphogenic protein meniscus replacements. Implantable prostheses.
Radiology	
Boron neutron capture therapy. Hyperthermia systems and applicators.	Image guided surgery.



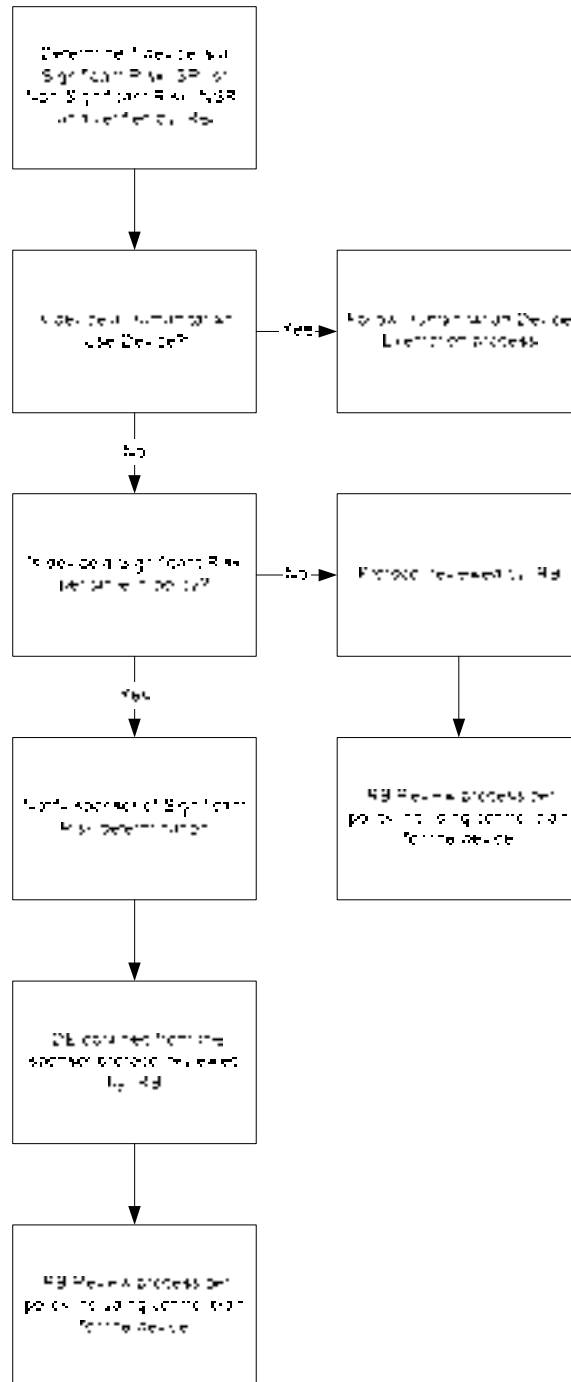
Appendix B

Examples of Non-Significant Risk Devices (not inclusive)

Lower power lasers for pain treatment. Caries removal solution. Contact lens solutions not used in eyes. Conventional GI and urology endoscopes. Conventional laparoscopes, culdoscopes, and hysteroscopes. Dental filling materials, cushions, pads. Denture repair kits and realigners. Digital mammography. Electroencephalography. External monitors for insulin reactions.	Functional electrical neuromuscular stimulators. General biliary catheters. General urological catheters. Jaundice monitoring for infants. MRI devices within FDA specified parameters. Nonimplantable electrical incontinence devices. OB/GYN diagnostic ultrasound. Wound dressings.
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INVESTIGATIONAL DEVICES

CD-102018 - HEALTHCARE OF ATLANTA





Administrative and Operational Policies and Procedures

Page 1 of 9

Policy Number:	1.57	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	
Title:	Data and Safety Monitoring of Clinical Research Studies	Date Revised:	
Regulatory Agency:			

I. POLICY:

The purpose of this policy is to assure that clinical research subjects are not exposed to unnecessary or unreasonable risks and that the investigator conducts the clinical trial according to the highest scientific and ethical standards by providing data safety monitoring plans for all clinical trials.

Definitions:

Data Safety Monitoring Plan: The collection, review, and analysis of data as the research study progresses to ensure the appropriateness of the research, its design and human subject protections.

Clinical Trial: Any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Data Safety Monitoring Committee (DSMC): A DSMC is an internal group established by the principal investigator (PI) and consists of individuals with expertise in the area of research who are not otherwise associated with the research study. The DSMC charge is to assess, at predetermined intervals, the progress of a research study, the safety data, and to recommend to the PI whether to continue, modify or stop a clinical trial based upon this review.

Data Safety Monitoring Board (DSMB): A DSMB is an external group established by the study sponsor or PI and consists of individuals with expertise in the area of research who are not otherwise associated with the research study. The DSMB charge is to assess, at predetermined intervals, the progress of a research study, the safety data, and to recommend to the sponsor whether to continue, modify or stop a clinical trial based upon this review.



II. PROCEDURE:

A. Principles of a Monitoring Plan

1. All clinical trials require monitoring, but not necessarily by a formal committee (DSMC or DSMB). Several factors are relevant to determining whether or not to establish a DSMC or DSMB for a particular trial:
 - a. Risk to trial participants
 - b. Practicality of DSMC or DSMB review
 - c. Assurance of scientific validity
2. The IRB will review the data safety monitoring plan as a part of the initial submission.
3. The frequency, intensity and mechanism of monitoring depend on the level of risk and the size and complexity of the trial. The data monitoring will be performed according to a predetermined schedule.
4. Monitoring should provide information, as appropriate, concerning the performance of individual centers, interim results of the study for evidence of adverse events, and possible early termination of the study because of early attainment of study objectives, safety concerns, or inadequate performance.

B. Elements of a Monitoring Plan (Appendix A)

The monitoring plan will:

1. Define the authority of the monitoring individual(s) with regard to advising or making recommendations concerning continuation, revision or discontinuation of the research project.
2. Include the process for making such recommendations or decisions.
3. Include the specific procedures that will be used to monitor for and report adverse events, protocol violations and deviations.
4. Include timing and frequency of data analysis.
5. Include periodic assessment of the following:
 - a. Participant recruitment and retention, to assure the feasibility of meeting recruitment projections.
 - b. Data quality and timeliness.
 - c. Participant risk versus benefit, taking into consideration the impact of new scientific or therapeutic developments.
 - d. Study site performance.
 - e. The procedure and schedule for timely reporting to sponsors and the IRB.



C. DSMC Review Involvement in Monitoring Plans

1. The DSMC is required to meet and review the IRB-approved protocol prior to the initiation of study enrollment.
2. The data safety monitoring plan will stipulate:
 - a. The composition of the DSMC;
 - b. The frequency of DSMC meetings; and
 - c. The material to be reviewed at each meeting.
3. The DSMC is required to record minutes of the meetings. The minutes are to include the following:
 - a. Attendance;
 - b. Summary of the discussion; and
 - c. Findings (e.g., research may begin or continue, recruitment is halted, actions needed to re-open recruitment, etc.).
4. When the DSMC concludes that the protocol should continue unmodified, the DSMC will send the investigator and the IRB the minutes. No further action is required.
5. When the DSMC concludes that recruitment should be stopped:
 - a. The DSMC will send the investigator the minutes with directive to suspend recruitment immediately and the investigator will forward the recommendations to the IRB.
 - b. The IRB Chair or designee will review the DSMC recommendations, and if in agreement, the IRB will notify the investigator, in writing, affirming the DSMC action, and directing the investigator to submit an amendment to implement the required changes.
 - c. Depending on the nature of the changes, the amendment will receive expedited or full IRB review.
6. When the DSMC concludes that changes to the protocol and/or the informed consent are required but recruitment may continue:
 - a. The DSMC will send the investigator and the IRB minutes.
 - b. The IRB Chair or designee will review the DSMC recommendations, and if in agreement, the IRB will notify the investigator, in writing, to submit and amendment to implement the required changes.
 - c. Depending on the nature of the changes, the amendment will receive expedited or full IRB review.
7. The researcher is required to include all DSMC reports as attachments to the progress report at the time of continuing IRB review.



D. DSMB Review Involvement in Monitoring Plans

DSMB review will be determined and set up by the study sponsor.

III. REFERENCES:

NIH Guidance on Reporting Adverse Events
NIH Policy for Data and Safety Monitoring
45 CFR 46.103(5)
45 CFR 46.111(6)



Appendix A

Research Monitoring Plan Template

1. Does this study ***only*** involve use of existing data or specimens, anonymous surveys or behavioral observations?

- No – Complete the rest of this form and include with your IRB submission.
- Yes – Do not complete this form. This plan is not needed for your IRB submission.

2. Who will perform the safety monitoring?

<input type="checkbox"/>	<p>The study poses no more than minimal risk to subjects. The PI, external (i.e., company-sponsored) Data Safety Monitoring Committee (DSMC) or other designee will perform the safety monitoring. <i>(If selected, go to item 3)</i></p>
<input type="checkbox"/>	<p>The study poses more than minimal risk to subjects. An internal (i.e., Children's) Data Safety Monitoring Committee (DSMC) will perform the safety monitoring. The DSMC is established (select one):</p> <ul style="list-style-type: none"> <input type="checkbox"/> within the division where the research is focused <input type="checkbox"/> within the department where the research is focused <input type="checkbox"/> within a Children's affiliate, specifically: _____ <p><i>(If selected, go to item 4)</i></p>
<input type="checkbox"/>	<p>The study poses more than minimal risk to subjects. An external Data Safety Monitoring Board (DSMB) will perform the safety monitoring. The DSMB is established (select one):</p> <ul style="list-style-type: none"> <input type="checkbox"/> by the protocol sponsor <input type="checkbox"/> by the funding agency <p><i>(If selected, go to item 5)</i></p>

From this point forward, only complete the sections that are relevant to your study monitoring plan and enter "N/A" in any irrelevant sections.

3. Who on the Children's study team will perform safety assessments?

(Attach additional sheets as necessary.)

Name	Role on Study	Mailing Address, Telephone, Pager and Email
	Contact person and	



4. What is the composition and responsibilities of the internal DSMC?

(DSMC voting members shall not have conflicts of interests with this study or with study personnel. Any study personnel on the DSMC shall be non-voting members and shall not serve as Chair. Attach additional sheets as necessary.)

Name	Role on DSMC	Title and Institution Affiliation	Mailing Address, Telephone, Pager and Email
	Chair		

5. What is the composition and responsibilities of the external DSMB?

(DSMB voting members shall not have conflicts with this study or with study personnel, and the membership shall include an independent statistician. Any study personnel on the DSMB shall be non-voting members and shall not serve as Chair. If DSMB members' names are unavailable at the time of submission they shall be added as an amendment as soon as they are identified. If DSMB members' names are confidential, justify this practice and describe each member's role on the DSMB. Attach additional sheets as necessary.)

Name	Role on DSMB	Title and Institution / Company Affiliation	Check Contact Person
	Chair	Mailing Address, Telephone, Pager and Email:	<input type="checkbox"/>
	Statistician		<input type="checkbox"/>
			<input type="checkbox"/>
			<input type="checkbox"/>

6. What are the safety monitoring methods and intervals?

(Monitoring intervals vary depending upon size, complexity, risk of study. Typically, monitoring is more frequent for higher risk, complex studies. Below indicate the interval/frequency of monitoring, i.e. number of months or number of subjects enrolled. If monitoring frequency is complex and detailed, include a reference to the pages of the protocol, investigator brochure or IRB application in which the interval/frequency of evaluation is found.)



Data Evaluated <i>(check all that apply)</i>	Interval/Frequency of Evaluation
<input type="checkbox"/> Age-specific intervention(s)	
<input type="checkbox"/> Clinical test(s)	
<input type="checkbox"/> Interview and/or other subject contact	
<input type="checkbox"/> Physical exam and/or vital signs	
<input type="checkbox"/> Symptoms and/or performance status	
<input type="checkbox"/> Adverse events	
<input type="checkbox"/> Other study parameter(s), specifically:	

7. What scale is used to grade adverse events in this study?

In the table at the end of this section, identify what scale will be used to grade adverse events (AEs) and indicate the assessment of the relationship between the adverse event and the study procedures. Each study may have a unique approach to grading AEs and the PI should consult the parent protocol and/or funding source for specific grading scales. Below are suggested guidelines for the grading of AEs. In general, ad hoc scales are discouraged.

Example A: **Cancer Therapy Evaluation Program (CTEP) Common Toxicity Criteria (CTC III)**
Available at: <http://ctep.info.nih.gov>. See "Reporting Guidelines, Common Toxicity Criteria."

Example B: **Common Grading Scale**

- 0 No adverse event, within normal limits or not clinically significant
- 1 Mild AE, did not require treatment
- 2 Moderate AE, resolved with treatment
- 3 Severe AE, resulted in inability to carry on normal activities and required professional medical attention
- 4 Life threatening or disabling AE
- 5 Fatal AE

Example C: **FDA Scale**
Mild, Moderate, or Severe (i.e., death, life-threatening, necessitating or prolonging hospitalization.). Additional information available at:
http://a257.g.akamaitech.net/7/257/2422/12feb20041500/edocket.access.gpo.gov/cfr_2004/aprqr/21cfr312.32.htm.

<input type="checkbox"/>	AEs will be graded according to CTEP Common Toxicity Criteria III (CTC III)
<input type="checkbox"/>	AEs will be graded according to the Common 0-5 grading scale shown above
<input type="checkbox"/>	AEs will be graded according to the FDA scale
<input type="checkbox"/>	AEs will be graded using another system, specifically:



8. What attribution scale is used in this study?

<input type="checkbox"/>	The PI will determine the relationship of AEs to the study test procedures and/or agent as "not related," "possibly related," "related or probably related," or "unknown" using standard criteria for clinical trials.
<input type="checkbox"/>	The PI will use an alternative attribution scale, specifically:

9. What is the adverse event reporting plan?

Adverse events from this protocol need to be reported to the IRB and possibly other sponsoring agencies or regulatory bodies. Refer to the Research Adverse Event Reporting policy for guidelines on reporting adverse events (Policy # XX.XX) and indicate below all of those which apply.

<input type="checkbox"/>	National Institutes of Health (NIH)
<input type="checkbox"/>	Food and Drug Administration (FDA)
<input type="checkbox"/>	Other agency or sponsor, specifically:

10. What are the decision-making criteria regarding continuation, modification or termination (including early termination rules) of the study?

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11. What will interval statistical analysis entail?

As applicable, describe interval statistical analysis used in deciding to continue, modify, or terminate the study. This description should include a brief description of the statistical methods used to decide continuation status of the study and should indicate if the statistician a participant in the study is independent.

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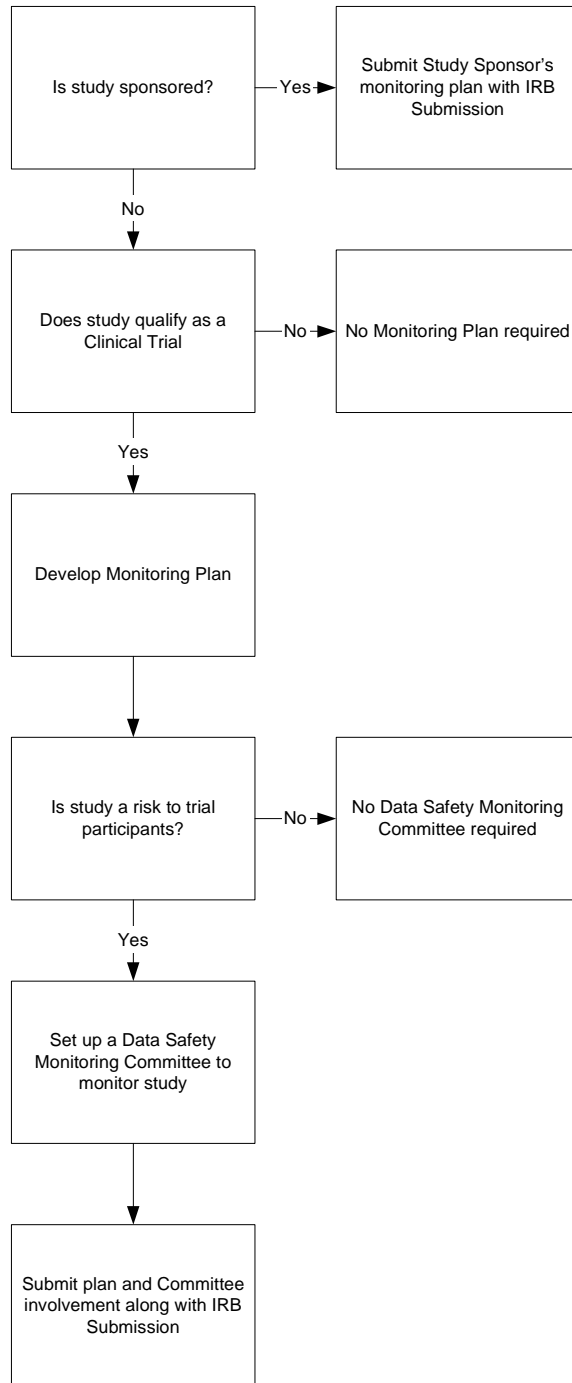
12. What is the method for documenting DSMB meetings or discussions?

As applicable, describe the method for documenting DSMB discussions and meeting minutes, as well as follow-up communications regarding the study. A summary and conclusions of the DSMB meeting need to be submitted to the IRB, but the detailed minutes do not, particularly for double-blind, randomized studies. Include in the description the timing of distribution of the DSMB report to the site investigator(s) and IRB(not to exceed 8 weeks). Also include information explaining how often the DSMB will meet.

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DATA AND SAFETY MONITORING OF CLINICAL RESEARCH STUDIES

CHILDREN'S HEALTHCARE OF ATLANTA





Administrative and Operational Policies and Procedures

Page 1 of 6

Policy Number:	1.58	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	
Title:	Conflict of Interest Related to Research	Date Revised:	
Regulatory Agency:	FDA, HHS, PHS, NSF		

Reference: #1.26 Responding to Allegations of Scientific Misconduct

I. **POLICY:**

Children's Healthcare of Atlanta (Children's) prohibits and avoids conflict of interest of its researchers by requiring full disclosure and openness of potential and actual conflicts of interest. This policy applies to all individuals conducting research at or otherwise involving Children's, as well as their spouses or dependent children, and covers all actual, apparent, perceived or potential conflicts of interest regardless of the research study's funding sources.

Definitions:

Conflict of Interest: Conflicts of interest refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in designing conducting, interpreting or reporting research.

Conflict of Interest Committee (COIC): The Conflict of Interest Committee oversees the Conflict of Interest Program by providing advice, assistance, and review services on specific written conflict of interest policies and procedures and related activities.

Investigator: For the purposes of this policy, this refers to any member of the research study staff.

II. **PROCEDURE:**

1. **Disclosure Process:** Investigators are required to sign a conflict of interest disclosure statement certifying that a conflict of interest does or does not exist, as follows:
 - a. Each time a new research study is submitted for Children's Institutional Review Board (IRB) for review and approval, the investigator shall complete the conflict of interest section in the appropriate Children's IRB form(s).
 - b. During the conduct of a research study, if any new financial or other interests are obtained by an investigator that may be construed to be a conflict, the investigator will notify the Children's IRB by submitting revised Children's IRB



form(s) which contain a conflict of interest section. This is particularly important if there is any change in personal financial or fiduciary status.

- c. Additionally, for research regulated by the U.S. Food and Drug Administration (FDA), study personnel are required to disclose conflicts of interest to the FDA and the Clinical Research department at the conclusion of the study and one year after.
- d. Third parties may report alleged conflicts, in writing to or calling, the Research Compliance Manager or by calling the Compliance Hotline (877-373-0126). Reports by a third party will be held in confidence and will follow the Children's operations policy [#1.04 Problem Reporting and Non-Retaliation](#).

For examples of conflicts of interest, see Appendix A.

2. **Review of Disclosures:** If the Children's IRB Office identifies a conflict of interest based on the information submitted it will forward the appropriate documentation for review by the Children's Conflict of Interest Committee (COIC). The COIC will review the documentation and recommend what conditions or restrictions, if any, should be imposed to manage, reduce or eliminate the conflict of interest. This recommendation will be forwarded to the Children's IRB Office and communicated to the Principal Investigator.

Recommendations may include the following:

- a. The research study is permitted with no requirement for modification because the disclosed information does not represent a possible source of unreasonable bias or inappropriate activity.
- b. The research study is permitted with the implementation of one or more modifications to preclude unreasonable levels of bias or inappropriate activities, with appropriate follow-up and review by the COIC and the Children's IRB. Possible modifications may include, but are not limited to:
 - i. Internal and external disclosure of relevant information;
 - ii. Reformulation of the research workplan;
 - iii. Close monitoring of the research project by independent reviewers (e.g., Data Safety and Monitoring Board);
 - iv. Reduction of financial interest or removal of fiduciary role;
 - v. Termination of a study personnel's involvement in the research;
 - vi. Severance of outside relationships (with supporting documentation or attestation) that pose conflicts;
 - vii. Implementation of measures and protective factors in the design of the study to minimize potential bias, such as multiple investigators, blinding, or objectives/endpoints; and



- viii. Restriction on investigator's role (e.g., cannot conduct the informed consent process or data analysis).
- c. The research study is prohibited from being conducted at or involving Children's due to an unacceptable conflict of interest. The research study cannot be approved by the Children's IRB or funding cannot be dispersed by the Children's Clinical Research Department until the COIC determines that the conflict of interest is managed, reduced or eliminated.
3. **Record Collection and Retention:** Children's IRB and the COIC will seek information on conflicts of interest only on a need-to-know basis and only as relevant to the research study under review. Records relating to conflicts of interest will be kept until three years after the termination of IRB approval or 2 years after the date of approval of the application of the drug, biologic, or device, or whichever is the longest period. The confidentiality of the investigators' private investments and personal finances will be protected. Information requested shall relate only to financial relationships that might influence the investigators' objectivity in conducting the research or creating the intellectual property. Examples of Complete Records:
- Records showing any financial interest or arrangement paid to investigator by sponsor of study
 - Records showing significant payments made by sponsor to investigator
 - Records showing any financial interests held by investigators
4. **Appeals Process:** The investigator may submit an appeal of the COIC determination to the Children's Senior Vice President of Medical Affairs. The Senior Vice President of Medical Affairs will seek expert opinions from individuals within or outside the Children's system. These opinions will be submitted to the Children's IRB Office and forwarded for review by the COIC. The COIC will reconsider the research study in view of the expert opinions and report its conclusion to the Children's IRB Office, the Principal Investigator, and the Senior Vice President of Medical Affairs.
5. **Failure to Disclose:** Failure to disclose a conflict of interest, including refusal to sign a disclosure statement or furnishing false, misleading or incomplete information, will lead to sanctions by Children's in accordance with the Children's operating policy [#1.26 Responding to Allegations of Scientific Misconduct](#). Sanctions may range from administrative intervention to termination of the research study.

Violations of federal or state statutes and guidelines regarding conflicts of interest shall be handled according to federal or state laws and requirements. For sponsored research, violations shall be reported to the study sponsor.



III. REFERENCES:

21 CFR 54 (a)(b), 2(f)

21 CFR 56.107

42 CFR 50

45 CFR 46

45 CFR 94

NIH Guidelines (A Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH) – January 2005

FDA Guidance (Financial Disclosure by Clinical Investigators) – March 2001

HHS Guidance (Financial Relationships and Interests in Research Involving Human Subject: Guidance for Human Subject Protection) – May 2004



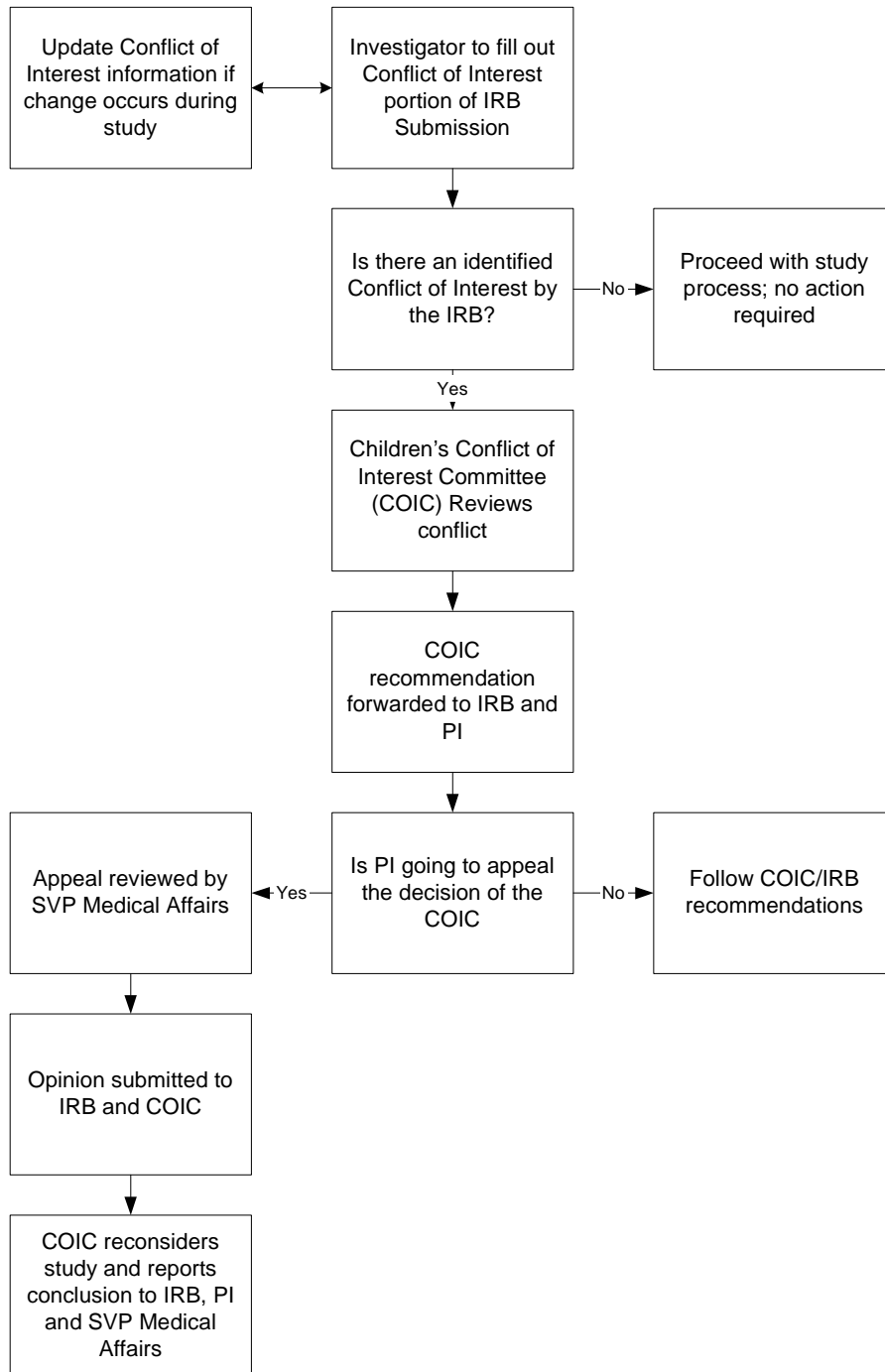
Appendix A

CONFLICT EXAMPLES (NIH and FDA Guidance)

- An investigator or his/her spouse/dependent children serving as director, officer or other decision-maker for a commercial sponsor of the research
- An investigator or his/her spouse/dependent children holding any stock or stock options in a commercial sponsor of the research (unless held in a diversified, independently managed mutual fund); FDA defines this as any equity interest that exceeds \$50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study
- An investigator or his/her spouse/dependent children having equity interests (e.g., stocks, stock options or other ownership interests) that when aggregated for the investigator and the investigator's spouse and dependent children, exceeds \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value and more than five percent ownership interest in any single entity
- An investigator or his/her spouse/dependent children receiving compensation for service as consultant or advisor to a commercial sponsor of research (excluding expenses), or receiving payments (or the institution receiving payments) from the sponsor to support activities that have a monetary value of more than \$25,000 exclusive of the costs of conducting the clinical study
- An investigator or his/her spouse/dependent children receiving honoraria from a commercial sponsor of the research
- An investigator or his/her spouse/dependent children personally accepting payment from the research sponsor for non-research travel or gifts (excluding government receipt of in-kind, research-related travel)
- An investigator or his/her spouse/dependent children obtaining royalties or being personally named as an inventor on patents or invention reports for the product(s) evaluated in the research or products that could benefit or result from the research
- An investigator or his/her spouse/dependent children receiving compensation that is higher for a favorable outcome than for an unfavorable outcome
- An investigator or his/her spouse/dependent children having personal or outside relationships with commercial sponsors of the research
- An investigator having financial interest in companies with similar products known to the investigator to be competing with the product under study

CONFLICT OF INTEREST PROCESS

Children's Healthcare of Atlanta





Administrative and Operational Policies and Procedures

Policy Number:	1.59	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	October 27, 2006
Title:	Research Adverse Event Reporting	Date Revised:	October 27, 2006
Regulatory Agency:			

I. POLICY:

In accordance with the Department of Health and Human Services resolutions governing human subject research and the Food and Drug Administration (FDA), Children's Healthcare of Atlanta is required to conduct continuing review of research. Included in the continuing review IRB process is the ongoing monitoring of adverse reactions and unexpected events. An Adverse Event (AE) will be reported at any time throughout the conduct of study protocol at or including Children's.

Definitions:

Adverse Event (AE): Any unintended and unfavorable sign, symptom, abnormality, or condition in a subject enrolled in a clinical investigation that does not necessarily have a causal relationship with the study procedures (See Appendix A, B, C and D for examples).

Expected or Anticipated AE: An adverse event previously known or anticipated to result from:

- the interventions and interactions used in the research;
- the collection of identifiable private information under the research;
- an underlying disease, disorder, or condition of the human subject; and/or
- other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Unexpected or Unanticipated AE: An adverse event not previously known or anticipated to result from:

- the interventions and interactions used in the research;
- the collection of identifiable private information under the research;
- an underlying disease, disorder, or condition of the human subject; and/or
- other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Serious AE: An adverse event characterized as any of the following outcomes:

- Death;
- Life threatening adverse experience;



- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- Congenital anomaly, birth defect or cancer;
- An overdose;
- Any medical event which required treatment to prevent one of the medical outcomes listed above;
- Any event that changes the risk/benefit ratio of the study;

Related AE: An adverse event for which there is a reasonable possibility that the AE may have been caused by the drug, device or intervention

Possibly Related AE: An adverse event that may have been caused by the study drug, device, or intervention; however there is insufficient information to determine the likelihood of this possibility

External AE: An adverse event experienced by subjects enrolled at sites other than Children's

Internal AE: An adverse event experienced by subjects enrolled at Children's

II. PROCEDURE:

1. Reporting to the IRB:

- a. These procedures apply to studies reviewed and approved by the Children's IRB; if Emory IRB serves as the IRB of record the Emory procedures apply.
- b. Unanticipated problems involving risks to human subjects or others in the conduct of the protocol shall be promptly reported by the investigator to the IRB no later than 10 working days of the investigator's knowledge of the occurrence. This includes unexpected adverse events that:
 - i. occur at a Children's study site or;
 - ii. occur at a non-Children's study site but affect the potential risk or benefits to Children's study site subjects and/or are required by the sponsor to be reviewed by Children's IRB.
- b. Documents to be submitted: The Children's IRB Office shall receive the following documents to allow for substantial and meaningful review of the event:
 - i. Serious Adverse Event Report Form. See Appendix E.
 - ii. A narrative describing the occurrence written in sufficient detail to allow for a thorough IRB evaluation.
 - iii. Any additional supporting documentation available to the investigator to aid in the IRB's consideration of whether the

event suggests adequate human subject protection mechanisms are in place or action is needed.

iv. Any study documents modified as a result of the occurrence.

These will be processed as an amendment to the study and the requirements for submission of requests for modification shall be followed.

- c. If the occurrence of the unexpected adverse event did not result in a modification of the study documents or procedures and the reporter deemed it non-substantive or not caused by the research procedures, then 2 collated copies of this information shall be submitted by the investigator and the report shall be forwarded for expedited review by the Children's IRB within 10 working days.
- d. If the occurrence of the unexpected adverse event resulted in a modification of the study documents or procedures and/or the reporter deemed it substantive or caused by the research procedures, then 20 collated copies of this information shall be submitted by the investigator and the report shall be forwarded for review by the convened Children's IRB within 10 working days.
- e. Failure to report an occurrence in a timely manner may result in temporary or permanent suspension of the research study at the Children's site.

2. Reporting to the Study Sponsor:

- a. Adverse events will be reported immediately to the sponsor (except for those events that the protocol or Clinical Investigator's brochure identifies as not needing immediate reporting). The sponsor protocol should indicate when and how adverse events are to be reported. It is likely that the sponsor will require this immediate report be followed promptly by detailed written reports of the event. PIs should contact the study sponsor for specific reporting requirements.
- b. If the study involves sponsored drug, device or biologics research the PI is required to report serious adverse events to the study sponsor as outlined in protocol or directed (internal adverse events) in addition to the IRB.

3. Reporting to the FDA:

- a. Pursuant to 21 CFR 312.32, adverse events that are both serious and unexpected will be reported to the FDA. In the case of industry-sponsored protocols, the sponsor will submit the FDA reports if the sponsor holds the IND or IDE. If the PI holds the IND or IDE, he/she reports directly to the FDA.
- b. In the case of PI-initiated research or research that does not involve funding from a sponsoring company, the PI of the protocol assumes the responsibility



to report adverse events to the FDA. In such instances, PIs follow the reporting procedure of the FDA Medical Products Reporting Program (MedWatch). Under the program, adverse events can be mailed, faxed, or reported online. The time requirement for MedWatch reporting varies according to the reporting method used (i.e. mailed, phone, faxed, or online). Additional information on the FDA MedWatch reporting can be obtained from the FDA web site <http://www.fda.gov/medwatch/index.html>

III. REFERENCES:

45 CFR 46.103 (b)(5)

45 CFR 46 Subpart A

21 CFR 56.108 (b)

21 CFR 312.64

21 CFR 312.66

21 CFR 312.32 (c)

21 CFR 803.30 Subpart C

NIH Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials

MDR – Medical Device Reporting Rule

Appendix A

Examples of Definitions of Adverse Events and Similar Terms

(1) Any undesirable and unintended, although not necessarily unexpected, effect of the research occurring in human subjects as a result of (a) the interventions and interactions used in the research; or (b) the collection of identifiable private information under the research.

[Adapted from the 1993 OPRR IRB Guidebook]

(2) Any occurrence of injury, dysfunction, disease, or abnormality of any organ or tissue that occurs in a human subject enrolled in a research protocol. Manifestations of an adverse event may include symptoms, physical exam abnormalities, diagnostic study abnormalities, and/or death. [Adapted from Walter Reed Army Medical Center – May 31, 2002 Policy for Reporting Adverse Events in Human Use Protocols]

(3) Any untoward medical occurrence in a human subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the product, whether or not considered related to the product.

[Adapted from International Conference on Harmonization guideline E2A]

(4) Any untoward sign, result, event, misadventure, injury, dysfunction, adverse drug reaction, or other undesirable happening that involves any human subject regardless of whether it was listed in the informed consent document as an expected risk. [Adapted from Naval Medical Research Center's March 26, 2002 Principles and Policies for the Ethical Protection of Human Subjects from Research Risks, chapter 14, paragraph 3(a)]

(5) Any untoward physical or psychological occurrence in a human subject participating in research. An adverse event can be any unfavorable or unintended event including abnormal laboratory finding, symptom, or disease associated with the research. An adverse event does not necessarily have to have a causal relationship with the research or any risk associated with the research or the research intervention, or the assessment. [Adapted from Veterans Health Administration Handbook 1200.5]

(6) An adverse drug experience as defined by FDA regulations at 21 CFR 314.80(a) - Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

(7) An adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of



a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action.

(8) A life-threatening adverse drug experience as defined by FDA regulations at 21 CFR 312.32 – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

(9) A life-threatening adverse experience as defined by FDA regulations at 21 CFR 600.80(a) – Any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred, i.e., it does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

(10) A serious adverse drug experience as defined by FDA regulations at 21 CFR 310.305(b), 312.32(a), and 314.80(a) – 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. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

(11) An unanticipated adverse device effect as defined by FDA regulations at 21 CFR 812.3(s) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

(12) An unexpected adverse drug experience as defined by FDA regulations at 21 CFR 312.32(a) – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by



virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Appendix B**Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations**

(1) A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen versus placebo combined with the current standard chemotherapy regimen for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is not an unanticipated problem because the risks of severe infections and death were anticipated.

(2) A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The investigator breaks the blind on the subject's study group assignment and learns that the subject was assigned to receive the active investigational agent. The protocol and informed consent document for the study indicated that there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the risk of gastric ulcers was anticipated.

(3) A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention. This example is not an unanticipated problem because the risk of stroke was



anticipated and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level. (NOTE: The assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event. In many cases, making a definitive determination regarding whether the frequency of a particular event is within the expected range is not possible.)

(4) A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to his underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research. This example is not an unanticipated problem because the subject's pulmonary embolus and death were clearly attributable to causes other than the research interventions.

(5) An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless sound proof booth and asked to wear headphones. The research protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. One subject enrolled in the research develops a severe anxiety reaction due to claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the risk of claustrophobic reactions was anticipated.

NOTE: For purposes of illustration, the case examples provided above represent generally clear-cut and unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it is not always clear whether a particular event is expected and whether an event is study-related.

Appendix C**Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations**

(1) A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the informed consent document for the study does not identify kidney damage as a risk of the research. The investigator breaks the blind for the subject's study group assignment and learns that the subject was randomized to the active investigational agent. Evaluation of the subject reveals no other obvious cause for acute renal failure. The subject is taken off the investigational agent and managed as an outpatient, and the subject's renal function returns to normal two weeks later. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the risk of acute renal failure was unforeseen.

(2) A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the informed consent document for the study does not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the risk of hematologic toxicity was unforeseen.

(3) The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of liver enzymes on serum chemistry tests in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because (a) although the risk of

mild liver injury was foreseen, severe liver injury resulting in hepatic failure was unforeseen; and (b) consideration of changes to the research protocol and the informed consent process is warranted.

(4) Subjects with coronary artery disease presenting with unstable angina are enrolled in a clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the informed consent document. After the first 20 subjects are enrolled in the study the investigators conduct an interim analysis and note that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate. This is an example of an unanticipated problem that must be reported because the investigators concluded that the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency.

(5) Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved informed consent document does not describe GERD as a risk of the research. Three of the first ten subjects are noted by the PI to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The PI determines that the GERD symptoms were most likely caused by the investigational drug, may alter the IRB's risk:benefit assessment, and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem because it altered the IRB's analysis of the risk versus potential benefit of the research and warranted consideration of substantive changes to the informed consent process/document.

(6) A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB Chairperson under an expedited review procedure. During the completion of the survey, one student subject has a severe psychological reaction manifested by intense sadness, depressed mood, and suicidal ideation. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not anticipated that such reactions would be triggered by the survey questions. This is an



example of an adverse event occurring in the context of social and behavioral research that was not anticipated because the risk of the negative psychological reaction was not foreseen, and consideration of changes to the research survey and the informed consent process is warranted. It is therefore an unanticipated problem that must be reported.

NOTE: For purposes of illustration, the case examples provided above represent generally clear-cut and unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes that it is not always clear whether a particular event is expected and whether an event is study-related.

Appendix D**Examples of Unanticipated Problems that Do Not Involve Adverse Events**

(1) An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on her way home from work. This is an unanticipated problem that must be reported because the investigators did not anticipate the theft and the subjects have been placed at significantly greater risk of harm from the breach in confidentiality of the study data.

(2) As a result of a processing error by a pharmacy technician, a subject enrolled in a clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem that must be reported.

(3) Subjects with cancer are enrolled in a phase II clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the Human Immunodeficiency Virus and the Hepatitis B virus. This constitutes an unanticipated problem that must be reported.

The events described in the above examples were unexpected and resulted in new circumstances that increased the risk of harm to subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the sponsoring agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).



Institutional Review Board
 1711 Tullie Circle, Atlanta, Georgia 30329
 Phone: (404) 785-7503 Fax: (404) 785-7512
<http://www.choa.org/clinicalresearch>

Report of Serious Adverse Event (SAE)

At a Children's Location

*SAE's which are expected and not considered serious should not be reported to the Children's IRB.
 Federal guidelines require timely reporting (within 10 days) of Serious Adverse Events*

IRB No.:	Principal Investigator (PI):	Address:																
Phone:	Research Coordinator:	Phone: Fax:																
Title:																		
Date of SAE: Subject's Initials or Study #	Type of Report: <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up Report #:																	
Number of Subjects currently enrolled at Children's: Number of SAE's that have occurred at Children's: Research involved a <input type="checkbox"/> Drug <input type="checkbox"/> Device <input type="checkbox"/> Procedure Name of Drug or Device: Has this type of SAE been reported before? <input type="checkbox"/> Yes <input type="checkbox"/> No Could this type of SAE occur again? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly <input type="checkbox"/> Unknown Has the SAE been reported to the Sponsor/Federal Agency? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, Date reported: _____ The SAE occurred: <input type="checkbox"/> within 30 days of treatment. <input type="checkbox"/> More than 30 days after treatment began. <input type="checkbox"/> More than 30 days after treatment was stopped.	<p>Check one of the following. Was the event associated with or the cause of any of the following? If other, provide a brief description.</p> <table border="0"> <tr> <td><input type="checkbox"/> Death</td> <td><input type="checkbox"/> Life Threatening Event</td> </tr> <tr> <td><input type="checkbox"/> New Cancer</td> <td><input type="checkbox"/> Significant Overdose</td> </tr> <tr> <td><input type="checkbox"/> Severe or Permanent Disability</td> <td><input type="checkbox"/> Hospitalization</td> </tr> <tr> <td><input type="checkbox"/> Congenital Abnormality</td> <td><input type="checkbox"/> Extended Hospitalization</td> </tr> <tr> <td><input type="checkbox"/> Other unexpected toxicity</td> <td><input type="checkbox"/> Other</td> </tr> </table> <hr/> <p>Check one of the following. What is the likelihood that this SAE was caused by the drug, device or procedure?</p> <table border="0"> <tr> <td><input type="checkbox"/> Definitely Yes</td> <td><input type="checkbox"/> Definitely No</td> </tr> <tr> <td><input type="checkbox"/> Probably Yes</td> <td><input type="checkbox"/> Probably No</td> </tr> <tr> <td><input type="checkbox"/> Possibly</td> <td><input type="checkbox"/> Unknown</td> </tr> </table> <p>Does this SAE change the risk/benefit ratio: <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Has the consent form been revised as a result of the SAE? <input type="checkbox"/> Yes <input type="checkbox"/> No</p>		<input type="checkbox"/> Death	<input type="checkbox"/> Life Threatening Event	<input type="checkbox"/> New Cancer	<input type="checkbox"/> Significant Overdose	<input type="checkbox"/> Severe or Permanent Disability	<input type="checkbox"/> Hospitalization	<input type="checkbox"/> Congenital Abnormality	<input type="checkbox"/> Extended Hospitalization	<input type="checkbox"/> Other unexpected toxicity	<input type="checkbox"/> Other	<input type="checkbox"/> Definitely Yes	<input type="checkbox"/> Definitely No	<input type="checkbox"/> Probably Yes	<input type="checkbox"/> Probably No	<input type="checkbox"/> Possibly	<input type="checkbox"/> Unknown
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<input type="checkbox"/> Definitely Yes	<input type="checkbox"/> Definitely No																	
<input type="checkbox"/> Probably Yes	<input type="checkbox"/> Probably No																	
<input type="checkbox"/> Possibly	<input type="checkbox"/> Unknown																	

Complete the following:

- If consent has not been revised, please explain why changes to the consent form are unnecessary based on the SAE.
- Check here indicating that you have included a narrative and supporting documentation. **A NARRATIVE, AND SUPPORTING DOCUMENTATION DESCRIBING THE SAE, MUST ACCOMPANY THIS FORM.**

PI Signature: _____

Date: _____

*****TO BE COMPLETED BY THE INSTITUTIONAL REVIEW BOARD (IRB)*****

SAE received on _____

Action taken by the Institutional Review Board: _____ Acknowledged _____ Request consent change
 _____ Other _____ See Attached

 Children's IRB Chair, Vice Chair or Their Designee

 Date



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Report of Serious Adverse Event (SAE)

At a Non-Children's Location

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Federal guidelines require timely reporting (within 10 days) of Serious Adverse Events*

IRB #:	Principal Investigator:	Address:
Phone:	Research Coordinator:	Phone: Fax:
Title:		
<p>1. Date (of Receipt) of reported Non-Children's SAE:</p> <p>2. Type of Report: <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up</p> <p>3. Report #:</p> <p>4. Does the Sponsor (or you) think that these serious adverse events warrant a temporary suspension of enrollment pending further analysis of the SAE? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>5. Does the reported SAE change the risk-benefit ratio? <input type="checkbox"/> Yes <input type="checkbox"/> No</p>		<p>6. Does the consent form need to be changed as a result of the reported serious adverse event? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes, attach a copy of the revised consent form, including the revision date, with changes high lighted.</p> <p>7. Does the protocol need to be changed as a result of the serious adverse event? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><i>If yes, attach a copy of the revised protocol.</i></p> <p>8. Attach a copy of the SAE or IND Safety Report.</p>

PI Signature: _____

Date: _____

TO BE COMPLETED BY THE INSTITUTIONAL REVIEW BOARD

SAE received on _____

Action taken by the Institutional Review Board:
change

_____ Acknowledged _____ Request consent

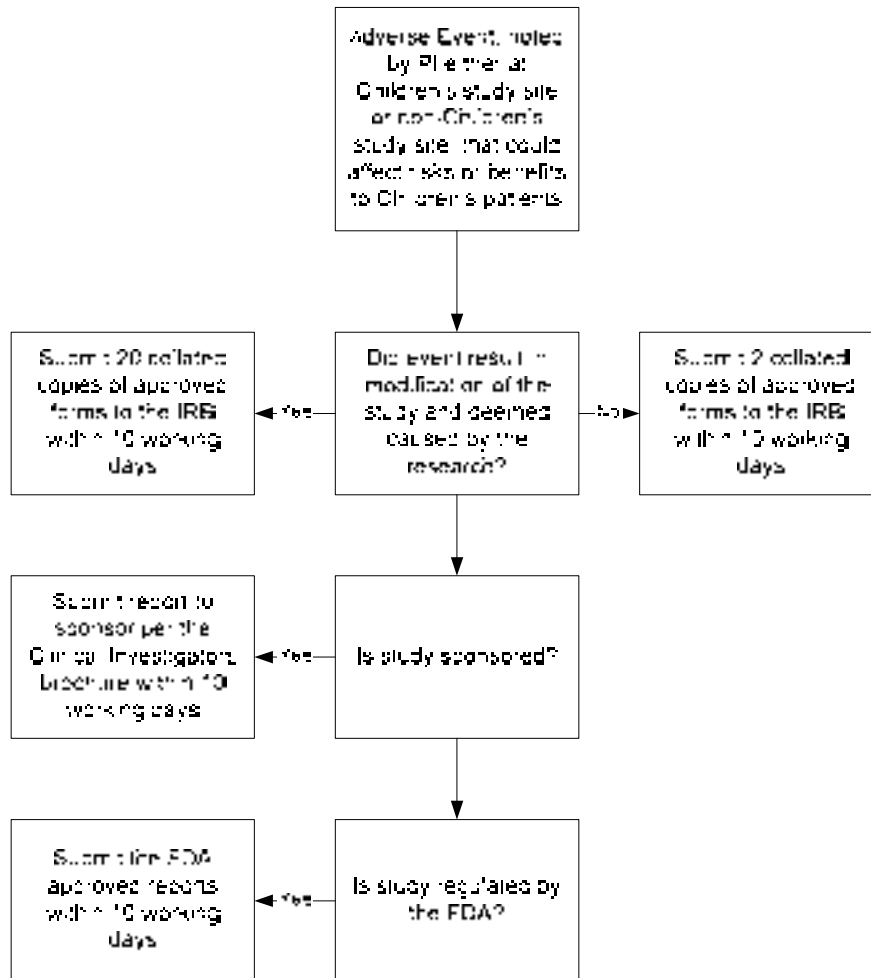
_____ Other _____ See Attached

Children's IRB Chair, Vice Chair or Their Designee

Date

Research Adverse Event Reporting

Children's Healthcare of Atlanta





Administrative and Operational Policies and Procedures

Page 1 of 6

Policy Number:	1.60	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	
Title:	Emergency Use of Investigational Drugs, Biological Products and Devices	Date Revised:	
Regulatory Agency:			

I. POLICY:

Children's Healthcare of Atlanta (Children's) supports a physician's obligations to treat a seriously ill patient with all available modalities. This policy aims to (i) support physicians by clarifying the strict emergency use requirements and (ii) outline the necessary procedures to help ensure Children's is in full compliance with those requirements when investigational test articles are used on an emergency basis with and without research intent.

II. DEFINITIONS:

Emergency use: The use of an investigational drug, biological product or device with a human subject in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

Investigational drug, biological product or device (i.e., test article): Products (i) not approved for use or marketing by the FDA or (ii) already approved by the FDA for specific indications that are being studied for different indications, doses, strengths, or frequencies other than those that have been FDA-approved.

Life-threatening: Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely debilitating: Disease or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.



II. PROCEDURE:

A. Emergency Use Without Research Intent

In order for an investigational drug, biological product, or device (i.e., test article) to be used on an emergency basis when there is no research intent, the following criteria must be met:

1. The subject has a condition that is life-threatening or severely debilitating per the definitions of this policy;
2. No standard acceptable treatment is available to treat the condition;
3. IRB review of the request is conducted at a convened meeting and approval is issued prior to initiation of the treatment, unless it is not possible to convene a quorum within the time available (in that case the use must be reported to the IRB within 5 working days, but the IRB review of that report shall not be construed as IRB approval – see below for more information on what is to be reported);
4. The test article has not been used on an emergency basis at Children's and/or by Children's employees or medical staff without prospective approval by the convened IRB (this criteria may only be waived if the only obstacle to providing the treatment to a second individual is that the IRB has not had sufficient time to convene a meeting to review the issue and it is inappropriate to deny emergency treatment to the second individual based on that);
5. The investigator obtains informed consent of the subject or the subject's legally authorized representative, unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:
 - (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 legal representative; and
 - (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.

If prospective informed consent will not be obtained, the written evaluation by the investigator and independent physician justifying each of the above four criteria is needed prior to initiation of the treatment, unless the investigator determines that immediate use of the test article is required to preserve the subject's life and there is not sufficient time to obtain an independent physician's



determination that the four conditions above apply. In this case, the investigator alone may make the determination based on the above four criteria and initiate the treatment, however determination of the investigator must later be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation and submitted to the IRB within 5 working days of the treatment. In any case, the written evaluation shall be dated and include a dated signature of the evaluating physicians.

In the report to the IRB, the investigator shall include the following information:

1. Date of the written report
2. Investigator's name, degree, employer, medical division/department, mailing address, email, and phone number
3. Name of the investigational test article
4. Name of the IND/IDE holder of the test article
5. Description and, as necessary, supporting documentation explaining in lay terms why the subject's condition is life-threatening or severely debilitating per the definitions of this policy
6. Description and, as necessary, supporting documentation explaining in lay terms why the subject's condition cannot be treated with standard acceptable treatments available to treat the condition (if there are none, this needs to be addressed)
7. Copy of the written informed consent document(s), or if the treatment already occurred and prospective informed consent was not obtained:
 - a. Copy of the written evaluation from the investigator and independent evaluating physician justifying how each of the required four criteria for a waiver was met; and
 - b. Independent physician's name, degree, employer, medical division/department, mailing address, email, and phone number
8. Statement that, to the investigator's knowledge, the test article has not been used on an emergency basis at Children's and/or by Children's employees or medical staff without prospective approval by the convened IRB, or a statement explaining why treatment needed to be initiated in a second individual prior to review and approval by the convened IRB.
9. If the report is being submitted after the treatment, a description of the subject's condition following treatment, including any adverse events or benefits observed.

B. Emergency Use With Research Intent

In order for an investigational drug, biological product, or device (i.e., test article) to be used on an emergency basis when there is research intent, the proposal must be reviewed and approved by the convened IRB. See Policy 1.16 (Institutional Review Board Standard Operating Procedures) for more information on applying for IRB review and approval of an initial protocol submission.



For planned research in emergent situations, prospective informed consent is required unless, in advance, the following has occurred:

1. The FDA issued approval of the waiver of the informed consent requirement;
2. The IRB issued approval of the waiver of the informed consent requirement after 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; and
3. The waiver of the informed consent requirement is publicly disclosed to the community in which the research will be conducted.

In order to qualify for a waiver of the prospective informed consent requirement in planned research emergent situations, the following criteria must be met:

1. The FDA has approved a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies the protocol as one that may include subjects who are unable to consent. The submission of that protocol 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. The application may not be submitted as an amendment to another IND/IDE application.
2. The human subjects have a condition that is life-threatening.
3. The available treatment(s) to treat the condition are unproven or unsatisfactory.
4. 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 the particular intervention.
5. Obtaining informed consent is not feasible because:
 - a. The subjects will not be able to give their informed consent as a result of their medical condition;
 - b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
6. Participation in the research provides the prospect of direct benefit to the subjects because:
 - a. Subjects are facing a life-threatening situation that necessitates intervention;
 - b. Appropriate 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
 - c. 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.
7. The clinical investigation could not practicably be carried out without the waiver of the informed consent requirement.
8. 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 shall summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

9. The IRB has reviewed and approved informed consent procedures and an informed consent document. 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.
10. Additional protections of the rights and welfare of the subjects are provided, including, at least:
 - a. 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;
 - b. 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;
 - c. 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;
 - d. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
 - e. 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 shall summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
11. Procedures are in place 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.
12. Procedures are in place 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.



13. Procedures are in place to inform the subject about the clinical investigation if his or her condition improves and previously only a legally authorized representative or family member was informed.
14. Procedures are in place to provide the subject's legally authorized representative or family member, if feasible, with information about the clinical investigation 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.

The following shall occur when a proposal is not approved by the IRB because it does not meet the criteria above:

1. The IRB shall provide these findings in writing promptly to the investigator and to the sponsor of the research.
2. The sponsor of the clinical investigation shall promptly disclose this information to (i) the FDA; (ii) 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 (iii) other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

III. REFERENCE:

- 21 CFR 50.23(a) and (c)
- 21 CFR 50.24
- 21 CFR 56.102 (d) and (l)
- 21 CFR 56.104(c)
- 45 CFR 46.101(i)
- 45 CFR 46.116
- 45 CFR 46.117
- FDA Information Sheets (1998 Update, p. 52)
- OPRR Report on "Emergency Medical Care" (May 15, 1991)
- OPRR Report on "Subject Informed Consent Requirements in Emergency Research" (October 31, 1996)



Policy Number:	1.61	Original Date Issued:	May 11, 2006
Section:	Operations	Date Reviewed:	November 7, 2007
Title:	Assent and Legally Authorized Representative Permission in Pediatric Research	Date Revised:	November 7, 2007
Regulatory Agency:			

I. POLICY:

This policy provides a framework to facilitate the development of an inclusive and respectful decision-making process with regard to child assent and parental permission for a child to participate in research.

Definitions

Child Assent: The affirmative agreement of a person under 18 years of age to participate in research.

Parental Permission: The affirmative agreement of parent(s) or legal guardian(s) to the participation of their child or ward in research.

II. PROCEDURE:

A. Assent Requirements Based on Age (parental permission required in all cases); see Section II (C) for exceptions:

1. Ages 5 and under: No assent is required.
2. Ages 6-10: Oral assent is required, written documentation of assent is not. The assent process shall cover orally in age-appropriate language all elements of the IRB assent form template (see Appendix A). Use template as guidance only.
3. Ages 11-17: Written documentation of assent is required using an age-appropriate form (see Appendix A).

B. Assent Process Elements: The assent process shall include at least the following elements:

1. Helping subjects achieve a developmentally appropriate awareness of the nature of their condition.
2. Telling subjects what they can expect from the research procedures.



3. Making a clinical assessment of subjects' understanding of the situation and the factors influencing how they are responding, including whether there is inappropriate pressure to accept research procedures.
 4. Soliciting an expression of subjects' willingness to accept the proposed research procedures prior to enrollment.
 5. Indicating what will be done if subjects decline to participate in the research procedures.
- C. Waiver of Assent Requirements:
1. If a waiver of any or all of the informed consent requirements are appropriate for the research study as confirmed by the IRB, then it is implied that a waiver of the assent requirements are appropriate as well. See Policy 1.16 Institutional Review Board Standard Operating Procedures for information on applying for a waiver of any or all of the informed consent requirements.
 2. If the research offers the possibility of direct benefit that is important to the child's health or well being and is available only in the context of research then a waiver of the assent requirements may be found appropriate, as confirmed by the IRB. In this instance, investigators shall obtain parental permission for the child's participation in the study and fully inform the child about the research (possibly including the use of an age-appropriate Information Sheet that explains the nature of the child's participation, as determined appropriate by the Principal Investigator and IRB).
- D. Parental Permission/Consent:
1. Investigators will seek informed permission of parents before involving a patient in a research study.
 2. The informed permission of parents includes all of the elements of standard informed consent, as outlined in policy 1.16 Institutional Review Board Standard Operating Procedures, section XV, Informed Consent.

III. REFERENCES:

OHRP Guidance, "Special Protections for Children as Research Subjects" – May 26, 2005
45 CFR 46.116
45 CFR 46.117
45 CFR 46, Subpart D

Appendix A

Children's Healthcare of Atlanta Assent to be in a Research Study¹

Study Title: *[Include a simplified version of the research title]*

Why am I being asked to do this?

We are asking you to take part in a research study because we are trying to learn more about *[briefly outline the purpose of the study in language that is both appropriate to the child's maturity and age]*. We are inviting you to be in the study because *[state why the child is being asked to participate]*.

Why is this study being done?

[Outline what the study is about in language that is both appropriate to the child's maturity and age]

What will happen to me?

[Describe what will take place from the child's point of view in language that is both appropriate to the child's maturity and age. Specify what is being done for research vs. regular clinical care]

Will the study hurt?

[Describe any risks and how these risks will be minimized to the child that may result from participation in the research]

Will the study help me?

[Describe any benefits to the child from participation in the research]

What if I have any questions?

You can ask any questions that you have about the study. If you have any questions later, you can call me *[insert study doctor's telephone number]* or ask me next time.

Do my parents know about this?

Yes, this study was explained to your parents and they said that you could be in it. You can talk this over with them before you decide.

Do I have to be in the study?

¹ For use with prospective subjects ages 11 to 17

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 8, 2006 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

No, you do not have to be in the study. If you don't want to be in this study, just tell us. You can say yes now and change your mind later. It's up to you.

Writing your name on this page means that you agree to be in the study, and you know what will happen to you. If you decide to quit the study, just tell the person in charge.

_____ Printed Name of Research Subject	_____ Age	_____ Date of Birth
_____ Signature of Research Subject	_____ Date	_____ Time
_____ Signature of Person Obtaining Assent/Consent/Permission	_____ Date	_____ Time
_____ Signature of Witness	_____ Date	_____ Time
_____ Signature of Interpreter	_____ Date	_____ Time

In my opinion, the child is not able to assent to the study for the following reason: _____

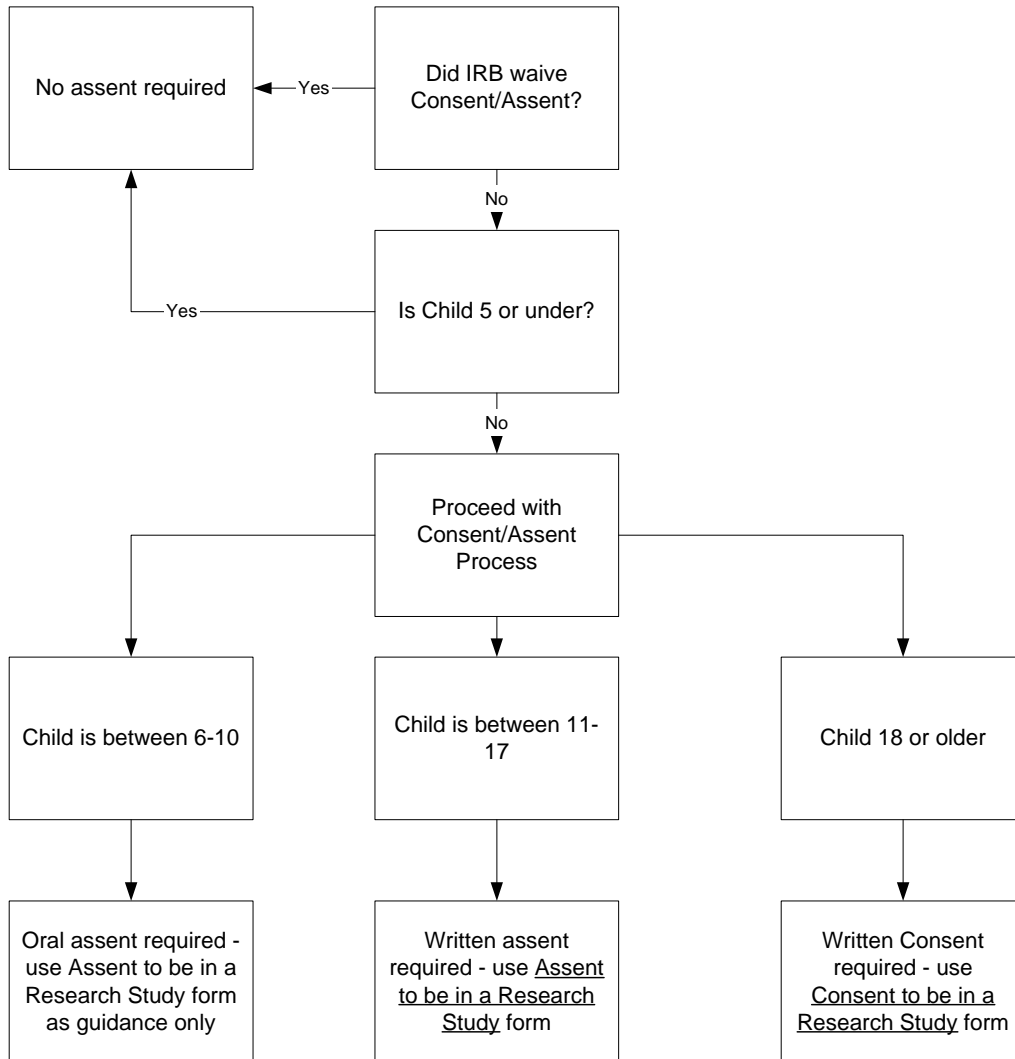
_____ Signature of Person Obtaining Assent/Consent/Permission	_____ Date	_____ Time
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CHOA IRB#:
Children's IRB Approval Date:
Children's IRB Expiration Date:

Template version date: March 8, 2006 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

ASSENT AND LEGALLY AUTHORIZED REPRESENTATIVE
PERMISSION IN PEDIATRIC RESEARCH

CHILDREN'S HEALTHCARE OF ATLANTA





Administrative and Operational Policies and Procedures

Policy Number:	1.62	Original Date Issued:	July 5, 2006
Section:	Operations	Date Reviewed:	October 27, 2006
Title:	Use of Human Biological Materials in Research	Date Revised:	October 27, 2006
Regulatory Agency:			

I. POLICY:

Definitions:

Unidentified Specimens (Repository Collections): For these specimens, identifiable personal information was not collected or, if collected, was not maintained and cannot be retrieved by the repository. Research using these specimens does not qualify as human subject's research.

Identified Specimens (Repository Collections): These specimens are linked to personal information in such a way that the person from whom the material was obtained could be identified by name, patient number, or clear pedigree location (i.e. his or her relationship to a family member whose identity is known).

Unidentified Samples: Sometimes termed "anonymous", these samples are from a collection of unidentified human biological specimens. Research using these samples does not qualify as human subject's research.

Unlinked Samples: Sometimes termed "anonymized," these samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being. Research using these samples does not qualify as human subject's research.

Coded Samples: Sometimes termed "linked" or "identifiable," these samples are from identified specimens with a code rather than with personally identifying information. Research using these samples does not qualify as human subject's research if the following conditions are met:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. the investigator(s) cannot readily ascertain the identify of the individuals(s) to whom the coded private information or specimens pertain.

If these conditions are not met, these samples quality as human subject's research.



Identified Samples: These types of samples are from identified specimens with a personal identifier that would allow the researcher to link the biological information derived from the research directly to the individual from whom the material was obtained. These samples qualify as human subjects research.

II. PROCEDURE:

Placement of Human Tissue into the Bio-Repository for Research Purposes

- A. Specimens may be stored in Children's Pathology Department freezers or departmental freezers but shall comply with applicable state and federal laws for proper storage of specimens.
- B. Human tissue may be placed into the appropriate bio-repository for research purposes. The tissue may be deposited via the following scenarios:
 1. *IRB Approved Protocol*: If human tissue is placed in a bio-repository as part of an approved IRB protocol (Children's or Emory, if the PI is Emory faculty), the tissue may only be used by the approved study staff. The IRB approved, protocol-specific consent form shall accompany the specimen (unless waived).
 2. *Operating Room*: If human tissue is obtained through standard operating room procedures and is placed into the bio-repository for potential research, a separate *Consent Form for the Use of Specimens in Research* (Attachment A) documenting consent of the donor shall accompany the specimen in addition to the standard surgical consent.
 3. *Standard Diagnostic and Treatment Procedures*: If tissue is obtained for purposes of diagnostic treatment and the remainder is stored in the bio-repository, a separate *Consent Form for the Use of Specimens in Research* (Attachment A) documenting consent of the donor shall accompany the specimen. For example, if tumor tissue is obtained for diagnostic purposes then discarded, no informed consent for use of the specimen for research is required. However, if the remaining tissue from a standard diagnostic test is banked for potential research use, an informed consent form documenting consent of the donor is required.
 4. *Tissue Acquired from Non-Children's Institutions*: If human tissue is acquired from an institution other than Children's for the purpose of tissue banking for research, the specimen shall be accompanied by an approved consent agreement signed by the tissue donor. The approved consent agreement must contain comparable language to the Children's *Consent Form for the Use of Specimens in Research* (Attachment A) and providing assurance that the tissue can be used without additional consent as long as donor confidentiality is maintained.
 5. *Tissue Sent to Non-Children's Institutions*: If human tissue is sent to another institution for research, the specimen shall either be de-identified or the donor's



agreement to this documented on a *Use of Specimens in Research* form (Attachment A).

Removal of Human Tissue from the Bio-Repository for Research Purposes

- A. Specimens may be released to qualified investigators after their proposals have been judged by a specialty review committee to assess scientific merit, clinical priority and feasibility and signed off by the Medical Director Anatomic Pathology - Egleston. The Review Committee shall be composed of a representative cross section of the Specialty that stored the tissue (Cardiology, Hem-Onc, Surgery, Pathology, etc.).
- B. The investigator will not to release the specimens or their derivative to any other laboratory without the express agreement of the Specialty Review Committee.
- C. Once the Specialty Review Committee approves the use of specimens, the investigator shall submit the protocol to the Children's IRB for approval or, if the PI is Emory faculty and a member of Children's medial staff, the Emory IRB for approval. Specimens will not be released without an IRB number and current IRB approval notice on file with the Bio-Repository.

Pre-existing Specimens

Children's acknowledges that there may be specimens that were collected prior to the development and enforcement of this policy. All human tissue deposited in the Pathology Bio-Repository after the effective date of this policy must conform to this policy. As it may be impractical to obtain informed consent for many specimens deposited before the effective date of this policy, the Pathology Bio-Repository will not be required to demonstrate evidence of informed consent for specimens collected prior to this date. Investigators will independently assure compliance with appropriate regulations and protocols which may apply to their pre-existing specimens.

REFERENCES:

National Bioethics Advisory Committee Guidance – August 1999
Children's Hospital of Los Angeles
21 CFR 312
21 CFR 812
21 CFR 50, 56



Attachment A

SAMPLE Consent Form for the Use of Specimens in Research

Your child is going to have [*Indicate procedure (e.g., surgery, biopsy, blood test)*] to [*treat or diagnose*] [*name of disorder*]. The doctor will remove (*type of sample*) to do some tests. (*Or, for example, "normally the tissue that is removed is discarded". Indicate if you are asking to remove additional specimen*). We would like to keep some of the (*type of specimen*) that is left over for future research. If you agree, this (*type of sample*) will be kept and may be used in research to learn more about [*name of disorder or type of disorders*].

Reports about the research done with your (*specimen*) will not (*Note: if reports will be given to the physician, indicate so here by changing the wording.*) be given to you or your child's doctor. These reports will not be put in your child's health record. The research will not have an effect on your child's care. Participation in this research is voluntary. Please read the information below and ask questions about anything that you do not understand before deciding whether or not to allow us to use the extra (*specimen*) for research.

Purpose of Obtaining the Tissue

- ♦ *State what the current study is designed to discover or establish.*
- ♦ *State if the purpose is to store the specimen for future research.*

Procedures

If you allow your child to be in this study, we will ask you to do the following things:

- ♦ *If additional procedures will be done (e.g., blood test, buccal smear, etc) describe them in this section.*
- ♦ *If you need to get information from the child's health records, indicate it here.*
- ♦ *If you will need to get permission to contact family members for more information, indicate it here.*
- ♦ *If no additional procedures will be done, this section can be deleted.*

Benefits

The research that may be done with your child's (*specimen*) will not directly benefit your child. However, the information that we learn from the research might help other children who have [*name of the disorder*] and other diseases in the future.



Potential Risks and Discomforts

The risk of allowing (*specimen*) for research is the unintentional release of information from your child's health records. The [*names of facilities storing samples*] will protect your records so that the name, address and phone number will be kept private, unless you give permission to do otherwise. The risk that this information will be given to someone is small.

Sometimes health records have been used by insurance companies to deny a patient insurance or employers may not hire someone with a certain illness. (*if the next applies insert here*) The results of genetic research may apply not only to your child but also to your other family members. This is why Children's will take careful steps to protect your research records.

♦ *If there are other risks associated with the procedures indicated above, indicate those risks here.*

Alternatives

You can choose not to have your tissue stored for research. Enough tissue needed for your care will still be kept. You can also choose not to allow use of your medical information.

Possible Commercial Products

Children's Healthcare of Atlanta (Children's) or another institution designated by Children's will own your child's sample. If a commercial product is developed from this research project, it will be owned Children's or an associated institution. You will not profit from the product.

Cells obtained from your child may be used to create a cell line which may be shared in the future with other researchers and which may be of commercial value. A cell line is a special set of cells that can grow for a long time in the laboratory. Cell lines can be useful because of the information we find out about certain diseases or because they may produce useful products.

Genetic research serves a number of purposes. These include medical knowledge, the development of new medications, tests and treatments and for public health tracking. Any medications, tests of treatments that may be developed might make money for Children's or its research partners, but you will not share in any of these profits. You will not be paid for the use of your blood, tissue, or the information that they contain.



Participation and Withdrawal

Participation in this research is voluntary. If you choose not to allow use to use your child's sample, it will not affect your relationship with Children's or your right to medical treatment or other services and benefits to which you would otherwise be entitled to. If you decide to participate, you are free to withdraw your consent and stop participating at any time without affecting your relationship with Children's. However, if you agree to have your sample shared with other researchers and later decide to withdraw, we may not be able to get back the entire sample.

How to Obtain Information

Daytime, Monday through Friday, 8:00 A.M. through 4:30 P.M. you may call Dr. *[Principal Investigator's name]* at *[phone]*.

Rights of Research Subjects

If you have questions regarding your child's rights as a research subject, you may contact the _____ (404) 785-_____.

Privacy and Confidentiality

Children's will take precautions to make sure that information about you/your child is kept private. Your child's name and other identifying information will be taken off anything associated with the (*specimen*) before it is provided to any other researcher, unless you give us permission to do otherwise. This will make it difficult for any research results to be linked to your child or your family.

Results or New Findings

The results of the studies of your samples may be made available to you or to your referring healthcare professional. It is your choice whether or not you want to know these results, and whether or not you want to have them reported to your health care provider for possible entry into your medical records.

Choices for Uses of Your Child's Information and Tissues

Please read the information below and indicate your choices for the use of your child's information and tissue.

1. My child's sample may be kept for use in research to learn about, prevent, or treat *[name of disorder]*.



Administrative and Operational Policies and Procedures

Page 7 of 9

Yes

No

2. My child's sample may be kept for use in research to learn about, prevent or treat other health problems (for example x,y,z).

Yes

No

3. My child's sample may be shared with other researchers to learn about, prevent or treat [name of disorder] or other health problems that may be unrelated to my child's illness.

Yes

No

4. My child's sample may be shared with other researchers to learn about, prevent or treat other health problems.

Yes

No

5. Someone from Children's may contact me in the future to take part in other research.

Yes

No

6. The research on your tissue is not set up to give results that are useful to you or your doctor. However, if such results are found, do you want us to try to contact your referring doctor or primary care physician?

Yes

No

7. (only if any of questions 1,2,3 were answered yes) My child's samples may be identified in the following way (Initial all that you agree to):

a. With my child's name and other identifying information. _____(initials)

b. With a code that is known only by Dr. [*Name*]. _____(initials)

c. My child's sample may be released to researchers outside of Children's Healthcare of Atlanta if there is no way to identify where it came from. _____(initials)



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SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

Your signature(s) below indicate

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You consent to your child's participation in this research study; and

Name of Subject

Name(s) of Parent(s)/Guardian

Signature of Parent (Guardian)

Date

Signature of Parent (Guardian)

Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject's parent(s)/guardian and answered all of his/her questions. I believe that he/she understands the information described in this document and freely gives permission for his/her child to participate.

Name of Investigator

Signature of Investigator

Date (must be the same date as subject's)

SIGNATURE OF WITNESS (If required by the Children's IRB)

My signature as witness certified that the parent(s)/guardian signed this permission form in my presence as his/her voluntary act and deed.

Name of Witness

Signature of Witness

Date (must be the same date as subject's)

Routing of signed copies of the consent form:

- 1) Give to parent or adult subject.
- 2) Place in the Children's Medical Record
- 3) Place in the Principal Investigator's research file.



Attachment A (continued)
Child's Assent for Use of Specimens in Research
Children's Healthcare of Atlanta

Why do you want to keep my extra tissue?

[briefly outline the reason that is both appropriate to the child's maturity and age]. We are inviting you to be in the future study because [state why the child is being asked to participate].

What will happen to me?

[Describe what will take place from the child's point of view in language that is both appropriate to the child's maturity and age]

Will it hurt?

[Describe any risks to the child that may result from participation in the tissue repository]

Will the study help me?

[Describe any benefits to the child from participation in the repository]

What if I have any questions?

You can ask any questions that you have about the future study. If you have a question later that you didn't think of now, you can call me *[insert study doctor's telephone number]* or ask me next time. *[If applicable: You may call me at any time to ask questions about your disease or treatment.]*

Do my parents know about this?

This was explained to your parents and they said that you could be in it. You can talk this over with them before you decide.

Do I have to be involved in this?

You do not have to be involved in this. No one will be upset if you don't want to do this. If you don't want to be involved in this, you just have to tell them. You can say yes now and change your mind later. It's up to you.

Writing your name on this page means that you agree to be in the study, and know what will happen to you. If you decide to quit the study all you have to do is tell the person in charge.

_____	_____	_____
Printed Name of Subject	Age	Date of Birth
_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Subject's Parent/Legal Guardian (Required for subjects under the age of 18 years)	Date	Time
_____	_____	_____
Signature of Person Obtaining Assent/Consent/Permission	Date	Time
_____	_____	_____
Signature of Witness	Date	Time



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Policy Number:	1.64	Original Date Issued:	September 22, 2006
Section:	Operations	Date Reviewed:	June 21, 2007
Title:	Oral Interpretation for Limited English Speaking (LES) Persons and Written Translation of Consent Forms for Research	Date Revised:	June 21, 2007
Regulatory Agency:			

Reference: Patient Care policy # 3.12 Admission Consent, Financial Consent and Informed Consent for Routine Procedures/Treatments

I. POLICY:

Children's Healthcare of Atlanta (Children's) recognizes the importance of ensuring opportunities for participation in research are not restricted based solely on capacity to speak English. This policy is designed to ensure that Limited English Speaking (LES) subjects are included in studies performed by Children's employed principal investigators or sponsored by Children's and properly consented per 45 CFR 46.116 and 21 CFR 50.20.

Definitions:

Limited English Speaking (LES) Person: One whose primary language is not English. This includes persons who have a limited ability to read and/or understand written or spoken English. For the purpose of this policy, LES also refers to Limited English Proficiency (LEP).

Interpreter: One who translates orally from one language into another.

Translator: One employed to render written works into another language.

II. PROCEDURE:

The Principal Investigator is ultimately responsible for ensuring each LES subject clearly understands the information presented.

A. Translation and Interpretation Requirements

1. If study staff anticipate encountering prospective subjects whose primary language is not English, then the research informed consent form must be available in that language.



2. Once the research consent is approved by the IRB, submit the approved consent to the Interpreting and Translating department for translation, then, submit the translated document to the IRB as a modification.
3. If study staff unexpectedly encounters a prospective subject whose primary language was not one anticipated at the initiation of the study, then a short form (Appendix A) may be used to document written informed consent provided the complete English language informed consent form is orally interpreted during the initial informed consent session and the prospective subject is provided with a copy of both the short form in their language and a complete informed consent form (per 45 CFR 46.117 and 21 CFR 50.27).
4. Short Forms:
 - The Children's Research Department website posts short forms in the most common languages encountered at Children's based on available data from the Children's Interpreting and Translation Service Department. These forms do not need to be included in submission packets to the IRB.
 - If study staff unexpectedly encounters a prospective subject whose primary language is one in which a short form is available through the Children's Research Department website then the appropriate short form may be printed and used by the study staff with no IRB review of this use required.
 - If study staff unexpectedly encounters a prospective subject whose primary language is one not available through the Children's Research Department website, then the English version of the short form shall be translated into that language, and that form shall be submitted to the IRB as a study modification and approved before use. For cases where the patient must be admitted to the study and cannot wait for IRB turnaround, the consent can be orally interpreted, with the signature and printed name of the interpreter included on the consent. Once the short form has been translated, send the translated form to the parent, if possible.
 - For assistance in translating documents, study staff will submit the document to be translated to the Children's Interpreting and Translation Services Department.
 - The IRB submission of the translated short form shall include a document indicating it was translated by a document translator.
 - Because of the number of studies which may include prospective subjects whose primary language is Spanish, a Spanish version of the Children's Informed Consent template is posted on the Research Department website to aid in the translation of the complete informed consent form to Spanish.
5. If use of an oral interpreter is required during the consent process, for other study procedures, or to answer questions or address concerns as they arise, the interpreter shall be a document translator whose documentation of certification is on file with the Children's Interpreting and Translation Services Department.



Study staff shall not use the subject's family, friends or staff as an interpreter for quality, safety, and confidentiality reasons. If one parent speaks English but the other does not, an interpreter is still required for quality and safety reasons.

6. For interpreting the full consent the PI will work with the interpreter in summarizing each section to be presented to the patient.
7. As part of the ongoing consent process, an interpreter shall be available to LES subjects to address questions or concerns. This availability shall coincide with the availability of the counterpart English-speaking study staff and be described in the IRB Submission.

B. Funding for the Translations

1. Corporate Sponsored Research: When research is sponsored by a corporate entity, the contract negotiated between the sponsor and Children's will include a provision for the sponsor to cover the costs of meeting these translation and oral interpretation requirements.
2. Federally/Privatey Funded Research: When research is federally or privately funded, the proposed budget will include a provision to cover the costs of meeting these translation and oral interpretation requirements as a direct expense.
3. No Funding: If the research is unfunded, the cost of translation is the responsibility of the investigator. If the investigator is a Children's employee, there will be no cost to translate the document.

III. REFERENCES:

45 CFR 46.111 (a)(3), 116,117
21 CFR 50.20-27

Appendix A (Short Research Consent Form)

Children's Healthcare of Atlanta
Assent/Consent to Participate in a Research Study¹

You are being asked to take part in a research study. The purpose of a research study is to find out how things work and gain new knowledge. A research study can be about:

- How the body works
- What causes disease
- How to treat disease
- What people think and feel about certain things

Before you decide whether to take part in this research study, you must be told about:

1. Why the research study is being done.
2. What will take place (called procedures).
3. How long the research will last.
4. Any procedures that are still being tested (experimental).
5. Any risks, discomforts, and benefits that may occur.
6. Any other helpful tests or treatment that may be possible
7. How your privacy will be kept.

When needed, you must also be told about:

1. Payment or medical treatment if injury or harm occurs
2. IF there are unknown risks
3. Times when the researcher may need to stop you from taking part in the study.
4. Any added costs to you.
5. What happens if you decide to stop taking part in the study.
6. When you will be told about new findings that may change your mind about being in the study.
7. How many people will be in the study.

If you agree to take part, you must be given a signed copy of this form. You will also receive a copy of the approved form for this study written in English.

You may call _____ at _____ any time you have questions. Also call about what to do if you are injured.

You may call the Children's Healthcare of Atlanta Institutional Review Board (IRB), at 404-785-7555 if you have any questions about your rights in this study. The IRB is a group of people who review human research studies in this hospital. They help protect the rights and welfare of people who take part in research studies.

If you decide not to take part in the study or to stop being in the study, it will not in any way affect your care at this hospital; not now, and not in the future.

¹If this form is being read by the legal guardian of a subject, "you" means "your child".

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 8, 2006 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)

Version Date: *[insert date form prepared]*

Your signature below shows that you:

- Have read this informed consent form
- Understand its meaning
- Have been given the chance to ask questions and are satisfied with the answers given to you.
- Agree to take part in this study and sign this informed consent form of your own free will.

You will be given a copy of the signed informed consent form.

_____ Printed Name of Research Subject	_____ Age	_____ Date of Birth
_____ Signature of Research Subject (Required unless research subject is under the age of 18 years and assent was not obtained for reason provided below)	_____ Date	_____ Time
_____ Signature of Research Subject's Parent/Legal Guardian (Required for research subjects under the age of 18 years)	_____ Date	_____ Time
_____ Signature of Research Subject's Parent/Legal Guardian (Required for research subjects under the age of 18 years when study poses more than minimal risk to the subject without the prospect of direct benefit)	_____ Date	_____ Time
_____ Signature of Person Obtaining Assent/Consent/Permission	_____ Date	_____ Time
_____ Signature of Witness	_____ Date	_____ Time

CHOA IRB#:

Children's IRB Approval Date:

Children's IRB Expiration Date:

Template version date: March 8, 2006 (NOTE: Delete this information when preparing your study's form, as well as all other information provided in italics throughout this form. The italicized information is part of the directions for completion of this form. The final version of this form that you submit should not include any italicized writing, unless that is your preference for emphasis of a specific point.)



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Policy Number:	8.01	Original Date Issued:	September 30, 2002
Section:	Information Management	Date Reviewed:	September 24, 2007
Title:	Electronic File Naming Policy	Date Revised:	May 7, 2004
Regulatory Agency:	HIPAA		

I. POLICY

To facilitate routine business and clinical activities employees may store PHI in databases, spreadsheets and other applications that are not part of Children's core systems. Under no circumstances should clinical processes be designed to be so dependent upon these satellite databases/spreadsheets that core systems and the original paper chart would not provide satisfactory backup in the event that the satellite database/spreadsheet was unavailable.

The intent of this policy is to ensure that the privacy and security of PHI is not compromised by the use of non-core data repositories of PHI.

DEFINITIONS

- 1. Core Systems:** Including but not limited to: EPIC, RIS, Mysis, IBEXSMS, Lawson, Sunquest, Pharmacy System, IDX or their successors.
- 2. Protected Health Information:** any individually identifiable information on a patient
- 3. Repository:** any electronic data storage file such as a database or spreadsheet
- 4. Share Folder:** a folder which is not a sub-folder of any other folder; a share folder is the highest level folder available on a drive
- 5. Sub-Folder:** a folder contained within another folder
- 6. Owner:** (a designated employee required for every folder or repository-containing PHI):
 - a. For a Share Folder** – is Director level or above who is clearly known by the Security Officer and is responsible for the creation of and access to the share folder
 - b. For a Sub-Folder** – is responsible for the creation of the subfolder and is identified in the title of the sub-folder
 - c. For a Repository** – is responsible for the creation of the repository and is clearly identified in the Properties/Author field or in the title of the repository



II. PROCEDURE

A. Share Folders containing PHI

1. Creation:
 - a. only for the purposes of treatment, payment or routine business operations
 - b. only by an owner as defined above for share folders.
2. Naming: will contain the suffix PHI in the title
3. Access:
 - a. Children's employees/physicians
 - i.) requiring such access for the purposes of treatment, payment or routine business operations
 - ii.) designated by the owner
 - iii.) approved by the Security Officer
 - b. Business Associates
 - i.) requiring such access for the purposes of treatment, payment or routine business operations
 - ii.) designated by the owner
 - iii.) confirmed to have a signed BA agreement in place and on file in Legal Services
 - c. All access must be
 - i.) restricted by Microsoft NT security to members with rights to the folder
 - ii.) updated annually by the owner in response to report generated from the Security Officer (Note: access control for terminated employees managed per separate policy)
4. Creation of sub-folders and repositories: only by the Owner of the Share Folder AND the Owner will validate the access to this new sub-folder or repository when it is created
5. Unauthorized Access or use: Anyone observed or otherwise found to have acquired or enabled unauthorized access to the repository will be counseled and corrective action taken. All episodes of inappropriate access will be reported to the Privacy Officer
6. Transfer of Information
 - a. Data may not be transferred from a repository to another location on the network without authorization from the Owner, The Security Officer, and appropriate password protection.
 - b. No one is authorized to make electronic copies of a repository containing PHI via tape, diskette or microfilm or other electronic medium without the knowledge of the Owner.



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- c. Hard copies of the data in a repository are governed by the policy: Guidelines for Copying Clinical and Business Information. (**Addendum A**)



Addendum A

Guidelines for Copying Clinical and Business Records

Pursuant to Children's Management of Hard Copy Records Policy, this document sets forth general guidelines applicable to all Children's employees, business associates, medical staff and trainees when copying protected health information and business information.

1. The person making copies of any protected clinical or business information is responsible for ensuring that all originals and copies are removed from the copying area.
2. Copies of any protected health information and business information should only be distributed to those individuals who have a determined right to access such information.
3. Anyone who provides copies of protected patient health information and business information inappropriately to an individual or entity is violating the law and shall be subject to Children's disciplinary process.
4. Any individual who finds protected health information or business information by a copying machine shall (a) if possible return the information to the owner (b) return to department supervisor (c) if clinical, return to medical records and (d) if non-clinical return to the Security Department.
5. Anyone finding confidential protected health information or business information that is unattended and in an inappropriate location (i.e. cafeteria, waiting room, outside the building, etc.) is asked to inform the Children's Privacy Officer.



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Policy Number:	8.15	Original Date Issued:	April 11, 2003
Section:	Information Management	Date Reviewed:	September 22, 2006
Title:	Uses and Disclosures for Research Purposes & Waivers (HIPAA Research Policy)	Date Revised:	September 22, 2006
Regulatory Agency:	HIPAA		

PURPOSE:

Additional privacy regulations have been promulgated under the Health Insurance Portability and Accountability Act (HIPAA) which directly impacts research involving human subjects. These regulations specify the conditions under which certain health information may be used or disclosed in research activities, including the conditions under which the individual patient's 'authorization' must be obtained. This policy and procedure specifies when Children's may use or disclose information about individuals for research purposes.

POLICY:

1. General

- a. Children's may use or disclose individual information for research purposes as specified in this policy.
- b. All such research disclosures are subject to applicable requirements of state and federal laws and regulations and to the specific requirements of this policy and related Children's policies. This policy is intended to supplement existing research requirements of the Common Rule, 45 CFR Part 46 and the Food and Drug Administration (FDA) Title 21, Part 50 and Title 21 Part 56 which govern human subjects research issues. This policy should be applied in jointly with the existing Institutional Review Board Standard Operating Procedures (Administrative and Operational Policy #1-16).
- c. De-identified information may be used or disclosed for purposes of research.
- d. A limited data set may be used or disclosed for purposes of research.
- e. Children's may also conduct or participate in public health studies (including registries and surveillance activities), studies that are required by law, and studies or analysis related to its health care operations. Such studies will be discussed in Sections 4 and 5 of this Policy.



2. Institutional Review Board (IRB) or Privacy Board established by Children's.

CHILDREN'S may use an IRB established in accordance with 45 CFR Part 46 or a Privacy Board that has been established by CHILDREN'S pursuant to this policy, to perform the duties and functions specified in this policy regarding a research project being conducted, in whole or in part, by CHILDREN'S or by a CHILDREN'S office or program.

3. Uses and disclosures for research purposes – specific requirements

a. CHILDREN'S may use or disclose client or participant information for research purposes with the client's specific written authorization. Such authorization must meet all the requirements described in the Use and Disclosure Policy, and may indicate as an expiration date such terms as "end of research study," "none," or similar language. An authorization for use and disclosure for a research study may be combined with any other type of written permission for the same research study, such as consent forms. If research includes treatment, the researcher may condition the participation in the research study on the provision of an authorization for use and disclosure of such research (See Appendix 1: Research Authorization Form).

b. CHILDREN'S may use or disclose client or participant information for research purposes without the client's or participant's written authorization, regardless of the source of funding for the research, provided that:

i. CHILDREN'S obtains documentation that a waiver of an individual's authorization for release of information requirements has been approved by either:

- A. An Institutional Review Board (IRB); or
- B. A privacy board as outlined in procedures 1(a-c).
- C. Mandatory documentation shall include all of the following: (1) identification of the IRB or privacy board, and date action was taken; (2) a statement that the IRB or privacy board has determined that the waiver of authorization satisfies all of the criteria required under the HIPAA Privacy rules; (3) a brief description of the specific information for which use and disclosure has been determined to be necessary for research by the IRB or privacy board; (4) a statement that the IRB or privacy board has conformed to normal or expedited review procedures, as applicable; and (5) the signature of the chair of the IRB or the privacy board (or his or her designee).
- D. Documentation of IRB or privacy board actions from outside institutions must meet our standards as documented in this policy and the related research policies (Administrative and Operational Policy #1-16).

ii. In some cases, a researcher may request access to individual information maintained by CHILDREN'S in preparation for research or to facilitate the development of a research protocol in anticipation of research. Before agreeing to provide such access



- to individual information, CHILDREN'S should determine whether federal or state law otherwise permits such use or disclosure without individual authorization or use of an IRB. If there is any doubt whether the use and disclosure of the information by the researcher falls within this HIPAA exception, review by an IRB or privacy board and formal waiver of authorization should be required. If such access falls within this HIPAA exception to authorization and is otherwise permitted by other federal or state law, CHILDREN'S may only provide such access if CHILDREN'S obtains, from the researcher, written representations that:
- A. Use or disclosure is sought solely to review an individual's protected information needed to prepare a research protocol or for similar purposes to prepare for the research project;
 - B. No client information will be removed from CHILDREN'S by the research in the course of the review; The client information for which use or access is sought is necessary for the research purposes;
 - C. Researcher and his or her agents agree not to use or further disclose the information other than as provided in the written agreement, and to use appropriate safeguards to prevent the use or disclosure of the information other than is provided for by the written agreement;
 - D. Researcher and his or her agents agree not to publicly identify the information or contact the individual whose data is being disclosed; and
 - E. Such other terms or conditions as may be required by applicable federal or state law.
- iii. In some cases, a researcher may request access to individual information maintained by CHILDREN'S about individuals who are deceased. CHILDREN'S should determine whether federal or state law otherwise permits such use or disclosure of information about decedents without individual authorization or use of an IRB. There may be instances where it would be inappropriate to disclose information, even where the individual subject of the information is dead – for example, families of individuals who died of AIDs may not have wanted such information to be disclosed at their deaths. If there is any doubt whether the use and disclosure of the information by the researcher falls within this HIPAA exception, review by an IRB or privacy board and formal waiver of authorization should be required. If such access falls within this HIPAA exception to authorization and is otherwise permitted by other federal or state law, CHILDREN'S may only provide such access if CHILDREN'S obtains the following written representations from the researcher:
- A. Representation that the use or disclosure is sought solely for research on the protected information of deceased persons;
 - B. Documentation, if CHILDREN'S so requests, of the death of such persons; and
 - C. Representation that the Individual's protected information for which use or disclosure is sought is necessary for the research purposes.
 - D. Researcher and his or her agents agree not to use or further disclose the information other than as provided in the written agreement, and to use appropriate safeguards to prevent the use or disclosure of the information other than is provided for by the written agreement;



- E. Researcher and his or her agents agree not to publicly identify the information or contact the personal representative or family members of the decedent; and
- F. Such other terms or conditions as may be required by applicable federal or state law.

4. CHILDREN'S Public Health Studies and Studies Required by Law

When CHILDREN'S is operating as an agent of a Public Health Authority (i.e., State, City or County Health Department, Centers for Disease Control and Prevention, etc.), CHILDREN'S is authorized to obtain and use individual information without authorization for the purpose of preventing injury or controlling disease and for the conduct of public health surveillance, investigations and interventions. In addition to these responsibilities, CHILDREN'S may collect, use or disclose information to the extent that such collection, use or disclosure is required by law without individual authorization. When CHILDREN'S uses information to conduct studies pursuant to such authority, no additional authorization is required nor does this policy require IRB or privacy board waiver of authorization based on the HIPAA Privacy rules. Other applicable laws and protocols continue to apply to such studies.

5. CHILDREN'S Studies Related to Health Care Operations

Studies and data analyses conducted for Children's own quality assurance purposes and to comply with reporting requirements applicable to federal or state funding requirements fall within the uses and disclosures that may be made without individual authorization as CHILDREN'S health care operations. Neither authorization nor IRB or privacy board waiver of authorization is required for studies or data analyses conducted by or on behalf of CHILDREN'S for purposes of health care operations, including any studies or analyses conducted to comply with reporting requirements applicable to federal or state funding requirements. "Health care operations" as defined in 45 CFR 164.512 includes:

- a. Conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities;
- b. Conducting population-based activities relating to improving health care or reducing health care costs, protocol development, case management and care coordination, contacting health care providers and patients with information about treatment alternatives; and related functions that do not include treatment;
- c. Reviewing the competence or qualifications of health care professionals, evaluating practitioner and provider performance, health plan performance, and conducting training programs, and accreditation, certification, licensing or credentialing activities;
- d. Underwriting, premium rating, and other activities related to the creation, renewal or replacement of a contract of health insurance or health benefits;
- e. Conducting or arranging for medical review, legal services, and auditing functions, including fraud and abuse detection and compliance programs;



- f. Business planning and development, such as conducting cost-management and planning related analyses related to managing and operating CHILDREN'S, including improvement of administration or development or improvement of methods of payment or coverage policies; and
- g. Business management and general administrative activities of CHILDREN'S, including management activities related to HIPAA implementation and compliance; customer services, including the provision of data analyses for policy holders, plan sponsors, or other customers; resolution of internal grievances; and
- h. Creating de-identified information or a limited data set.

PROCEDURES:

1. A IRB or privacy board must:
 - a. Have members with varying backgrounds and appropriate professional competency as needed to review the effect of the research protocol on the Individual's privacy rights and related concerns;
 - b. Include at least one member who is not affiliated with CHILDREN'S, not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any such entity; and
 - c. Does not have any member participating in a review of any project in which the member has a conflict of interest.
2. Documentation required of IRB or privacy board when granting approval of a waiver of an individual's authorization for release of information must include:
 - a. A statement identifying the IRB or privacy board that approved the waiver of an individual's authorization, and the date of such approval;
 - b. A statement that the IRB or privacy board has determined that the waiver of authorization, in whole or in part, satisfies the following criteria:
 - i. The use or disclosure of an individual's protected information involves no more than minimal risk to the privacy of individuals, based on at least the following elements:
 - A. An adequate plan to protect an individual's identifying information from improper use or disclosure;
 - B. An adequate plan to destroy an individual's identifying information at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
 - C. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the protected information would be permitted under this policy;



- ii. The research could not practicably be conducted without the waiver
- iii. The research could not practicably be conducted without access to and use of the Individual's protected information.
- c. A brief description of the protected health information for which use or access has been determined to be necessary by the IRB or privacy board;
- d. A statement that the waiver of an individual's authorization has been reviewed and approved under either normal or expedited review procedures, by either an IRB or a privacy board, pursuant to federal regulations at 45 CFR 164.512(2); and
- e. Documentation of the waiver of an individual's authorization must be signed by the chair, or other member as designated by the chair, of the IRB or the privacy board, as applicable.

REFERENCES:

- 45 CFR 164.512



Definition(s):

Authorization: Permission by an Individual, or his/her Personal Representative(s) for the release or use of information.

Business Associate: An entity or individual who, on behalf of CHILDREN'S, performs or assists in the function or provision of services for CHILDREN'S. Business associates do not include Licensees or Providers unless the Licensee or Provider also performs some service on behalf of CHILDREN'S.

Client (Patient): An Individual who requests or receives services from the Children's Healthcare of Atlanta, Inc.

Client (Patient) Information: Personal information relating to a CHILDREN'S client.

Client (Patient) Records: The collection and compilation of personal information about CHILDREN'S clients into one or more locations and in various forms, including information that is transmitted by electronic media.

Client (Patient) Services: The provision of assistance, care, treatment, training or support to a client by CHILDREN'S.

Collect / Collection: The assembling of personal information through interviews, forms, reports or other information sources.

Disclosure / Disclose: The process of releasing, relaying, provision of access to, or conveying client information to any individual or entity outside the Department.

Health Care: Involves care, services or supplies related to the health of an individual. Health Care includes: preventive, diagnostic, therapeutic, rehabilitative, maintenance, or palliative care and counseling services, assessment, or procedure with respect to the physical or mental condition, or functional status of an individual, or that affects the structure or function of the body.

Individual: The person who is the subject of information collected, used or disclosed by CHILDREN'S.

Institutional Review Board (IRB): A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research (CFR 46:102(g), 46:108, 46:109)



Marketing: Communication about a product or service that encourages persons receiving the communication to buy or use the product or service. There is no limit to the type or means of communication.

Minimum Necessary: When using or disclosing confidential client information, it is the process of making a reasonable effort to limit that information to the minimum necessary to accomplish the intended purpose of the use, disclosure or request.

Participant: Individuals participating in CHILDREN'S population-based programs, services and activities. Examples of "Participants" include but are not limited to: A person who is a subject of a research study or public health studies, immunization or cancer registries, newborn screening, and other health services.

Personal Representative: If under applicable law a person has authority to act on behalf of an Individual who is an adult or an emancipated minor in making decisions related to the program, service or activity, CHILDREN'S will treat that person as the personal representative of the Individual. If under applicable law a parent, guardian, or other person acting *in loco parentis* has authority to act on behalf of an Individual who is an unemancipated minor in making decisions related to the program, service or activity, CHILDREN'S will treat that person as the personal representative of the Individual. CHILDREN'S policy, procedure or rule may include requirements related to documentation of the authority of the Personal Representative.

Privacy Rights: The specific actions that an Individual can take or request to be taken with regard to the uses and disclosures of their information.

Research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

Use: The sharing, employment, application, utilization, examination, or analysis of information with CHILDREN'S.

Version Date:



Authorization to Release Protected Health Information for Research Purposes

Title:

Principal Investigator:

Sponsor's Name:

The Health Insurance Portability and Accountability Act (HIPAA) is a federal law passed to protect the privacy of your child's Protected Health Information (PHI). PHI is any information about your child that could tell someone else who your child is. "Researchers" are what we call the people who are conducting the study. Government agencies may also need to look at your child's health information; these agencies make rules and policies about how research is done. The Institutional Review Board (IRB) can also look at your child's health information. The IRB is a committee that reviews research to make sure your child's rights and welfare are protected while being in the study. Sponsors who pay for the research also have the right to review your child's health information. Your child's health information may be disclosed if a court of law should order it. We will not use or share your child's health information in any way other than what we explain in this form. We will keep your child's health information private to the extent allowed by law. We will use a study number or other code rather than your child's name on study records when we can. Your child's name or any other fact that might point to your child will not appear if we publish the study results or make a presentation about the study.

Signing this document means you allow the researchers conducting the research to use your child's health information for this research study. Below is a list of things that HIPAA defines as PHI, the boxes that have an 'X' in them is the PHI that we will collect.

What PHI will be collected for this study:

- | | |
|--|---|
| <input type="checkbox"/> Name | <input type="checkbox"/> Email or IP address |
| <input type="checkbox"/> Address | <input type="checkbox"/> Dates of admission, discharge, treatment or death |
| <input type="checkbox"/> Telephone # | <input type="checkbox"/> Health Plan #'s |
| <input type="checkbox"/> Date of Birth | <input type="checkbox"/> Full face photogenic images or comparable images |
| <input type="checkbox"/> Social Security # | <input type="checkbox"/> Certificate/License #'s |
| <input type="checkbox"/> Fax # | <input type="checkbox"/> Vehicle Identifiers, vehicle serial #'s or license plate #'s |
| <input type="checkbox"/> Medical Record # | <input type="checkbox"/> Device Identifiers and serials #'s |
| <input type="checkbox"/> Account # | <input type="checkbox"/> Biometric identifiers, including finger and voice prints |

What other information will be collected for this study:

Who will collect the information:

The research staff conducting this study will collect and copy the PHI described above. If any of the PHI is to be shared with other people, as described later in this section, then the research staff will be responsible for sharing the information.

Who else will see the information at this hospital or office:

- Children's Healthcare of Atlanta Institutional Review Board (IRB), the committee that oversees research studying people.
- Other people that work for Children's Healthcare of Atlanta who need the information to perform their job duties (for example, to provide treatment, to ensure the integrity of the research, or for accounting and billing matters).
- People that work at _____ where your child will be seen for office visits.
- Other people that work at _____ who need the information to perform their job duties.

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CHOA IRB#:

Children's IRB Approval Date:

Version Date:

- Office for Human Research Protections (OHRP), a government agency that makes rules and policies about how research is done.
- The Food and Drug Administration (FDA), another government agency that makes rules and policies about how research is done.
- IRB's at other places where this study is being conducted.

Other people outside of this hospital or office that may see the information:

In conducting this research, we may share your child's health information with people outside of this hospital or office. If your child's study record is looked at by any of these groups, they may also need to see your child's entire medical record. The health information that is shared with these groups may no longer be covered by the HIPAA regulations. These groups include:

It is your choice to let the researchers use and share your child's health information. You can, at any time, change your mind about the researchers using your child's health information. If you no longer want your child's health information used or shared you must make the request in writing by signing a "Request for Withdrawal of Authorization". The researcher will give you a copy of this form to sign. This is called "withdrawing your authorization". If you withdraw your authorization it will not affect your child's current or future health care at this hospital or office and there will be no penalty or loss of any benefits you may be otherwise entitled to. If you withdraw your authorization we will not be able to collect any new health information and your child will be withdrawn from the study. However, we can continue to use the health information we have already collected as needed to protect the integrity of the research. You have the right to look at the information we collect. However, the information from the results of the study will not be available during the study; it will be available after the study is finished.

This authorization expires: _____(insert applicable date or insert "no expiration designated").

You will receive a copy of this form.

Print Patient Name

Printed Name of Parent, Legal Guardian or Patient

Check one of the following:

- I am the parent
- I am the Legal Guardian (state relationship to patient): _____
- I am the patient (must be 18 years of age or older)

Signature of Parent, Legal Guardian or Patient

Date

Printed Name of Person Obtaining Authorization

Signature of Person Obtaining Authorization

Date

CHOA IRB#:

Children's IRB Approval Date:



Administrative and Operational Policies and Procedures

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Policy Number:	8.18	Original Date Issued:	May 19, 2004
Section:	Information Management	Date Reviewed:	January 23, 2008
Title:	Document Retention and Destruction	Date Revised:	January 23, 2008
Regulatory Agency:	TJC; HIPAA		

I. POLICY:

It is the policy of Children's that all clinical, administrative and business documents be retained in an orderly fashion, and in compliance with all applicable state and federal laws and regulations, stored properly and destroyed when appropriate or permanently archived depending on the nature of the documents and the requirements of law.

This policy applies to all forms of documentation, including hard copy and electronic.

Confidentiality of Protected Health Information will be maintained throughout the process of document retention and destruction.

II. PROCEDURE:

A. Document Creation

An organization, its officers and individual employees are accountable for decisions and actions taken in the normal business course of business. Every individual should be aware of the requirements for recordkeeping including compliance requirements. Creation of documents inappropriate for the business purpose of the organization or communicating information (written or orally) to individuals that do not have the right to know the information violate the standards of conduct and confidentiality policies of Children's. To assist in creating and handling information, we have established these procedures.

1. Employees shall create and organize all appropriate business records needed to meet operational and regulatory requirements. (Refer to appropriate policies/procedures regarding specific forms.)
2. All records will be created in a manner that ensures the records are accurate and identifiable.
3. Records should be created to document decisions and actions taken in the course of conducting business activities. The following are included as examples:



- a. Minutes of meetings [consult Office of General Counsel for format]
 - b. Employee personnel records
 - c. Patient care records
 - d. Tax records
 - e. Records of business and strategic decisions
 - f. Contracts/Agreements [see Contracting policy]
 - g. Accounting records
 - h. Audit reports
 - i. Leases [see Contracting policy]
 - j. Email communications [see Electronic Communications policy]
4. Records should be identifiable, retrievable, accessible and available as needed, but should be limited in circulation to those involved in a decision or process.
 5. Documents should be distributed to the smallest possible number of recipients.
 6. Appropriate authorization must be obtained before confidential records can be distributed, i.e., patient authorization for medical records, employee authorization to release information contained in the personnel file. (See related policies under HIPAA and employment).
 7. Individuals should be conscious of the risks of e-mail and electronic data storage. When creating e-mail messages, one should be aware that Children's has strict policies against inappropriate e-mail messages.

B. Document Retention

Children's complies with federal and state laws and regulations regulating specific record retention requirements.

1. The length of time a document (hard copy or electronic) must be kept depends on the purpose for which it is created. Answering the following questions may be helpful to classify a document:
 - A. How is the record made and from where did it originate?
 - B. What does it accomplish or establish?
 - C. What are the chances of it being needed? If needed, could it be reconstructed, and if so, how difficult would it be to do so?
 - D. Is the information available elsewhere?
 - E. How serious would it be if we were unable to put our hands on a particular record 5 or 10 years from now?
 - F. Does the record protect the rights of an individual or the organization?
 - G. Is there a law or regulation requiring the record to be kept?



2. Records may also be classified to determine their importance:
 - A. Vital Records: irreplaceable; do not have the same value as the original if reproduced.
 - B. Important Records: can be reproduced after much delay and at great expense.
 - C. Useful Records: cause some inconvenience if lost, but can be readily replaced.
 - D. Non-essential Records: serve no useful purpose and are eligible for destruction.
3. **When Legal Services or Compliance become aware of any internal or external investigation, claim or legal proceeding they will notify all parties regarding the need to suspend any scheduled destruction and to produce or retain all related documents.**
4. Children's will provide proper time periods for retention of documents by following the [Document Retention Schedule](#) which incorporates legal requirements for retention periods for various types of business records.
5. In addition to legal requirements for record retention periods, contractual obligations can also impact retention times. A contract archive is maintained in Legal Services, which also provides for record retention. Any records relating to a contractual obligation will be maintained in Legal Services.
6. All records affecting the regulatory obligations of the organization are maintained for a sufficient period to meet those requirements.
7. Records are stored in a manner which allows access and retrieval as the need arises. Paper files, electronic files and emails are destroyed when they are no longer required to be maintained for one of the above purposes.
8. Records should be destroyed at the earliest date permitted by law or policy. Documents sent to storage shall include a destruction date on their label.
9. All clinical records are maintained by Health Information Services under their departmental policies.
10. Central department filing and storage should include all organizational records. Individual desk files shall not be maintained.
11. Legal Services will maintain an original of each contract and agreement entered into on behalf of Children's and its subsidiaries.
12. Risk Management will retain copies of all insurance records and claim reports.



13. Purchasing will retain copies of all purchase orders and agreements relating to the acquisition of goods and services.
14. Human Resources will retain all employee records.
15. Policy Administrator will retain copies of Children's system policies.
16. Scanning and electronic storage is an acceptable way to retain records during the required retention time period. Any employee responsible for maintaining records must be familiar with confidentiality requirements.

C. Document Retention Schedule

The retention schedule was developed by incorporating statutory requirements and organizational needs. In those cases where contractual obligations or organizational needs lengthen the retention time period, specific reference will be made in the records retention log to identify the additional requirements.

D. Document Off-Site Storage

Children's will store records (those which are to be stored in the warehouse) in a clean, safe, and well-organized environment consistent with the [Document Retention Schedule](#). The system will allow for reasonable accessibility of stored documents.

Sending records for storage:

1. Contact Purchasing to determine where records should be sent for storage.
2. Each department is to box up files to be stored in storage boxes. The records contained in each box should be of the same type; different types of records in separate boxes.
3. Each box is to be labeled on the end panel by the responsible department with the date, contents, department and destruction date. Do not write any information on the box lid. A content list shall be placed in the box and also in the department central files describing which records are housed in each box.
4. Each department should keep one departmental log of all stored records.



V. Document Destruction

Proper timing and method for destruction of records assures that all forms and drafts of a document are properly destroyed. Documents will be destroyed at the earliest date permitted by law and as determined by business need. All confidential records must be completely destroyed either by secure shredding or incineration. Children's provides secure bins for documents that must be destroyed in confidence.

Procedure:

1. When allowed by the [Document Retention Schedule](#) records that are no longer required to be maintained will be destroyed.
2. Confidentiality of records shall be maintained through destruction.
3. Electronic copies of messages or documents are to be treated no differently than paper copies. Disks or backup tapes should be securely disposed of along with paper and electronic records that are scheduled for destruction.
4. A departmental log shall be maintained listing what was destroyed, when, and by whom.
5. If litigation is filed or a claim is made that relates to organizational documents, legal or compliance representatives will immediately notify document owners of the need to preserve all documents. The notified departments immediately must cease any scheduled destruction, preserve all records, and cooperate with legal to inventory and produce all required records.



Administrative and Operational Policies and Procedures

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Policy Number:	8.47	Original Date Issued:	July 5, 2006
Section:	Information Management	Date Reviewed:	
Title:	Research Record Storage, Retention, and Disposition of Documents/Records	Date Revised:	
Regulatory Agency:	HIPAA, JCAHO		

I. POLICY:

This policy outlines the requirements for orderly retention and appropriate destruction or permanent archive of research documents per the requirements of applicable state and federal laws and regulations. This policy applies to:

- (i) all forms of research documentation, whether physical or electronic;
- (ii) all Children's employees and medical staff and any other persons at Children's involved in the design, conduct or reporting of research at or under the auspices of Children's; and
- (iii) all research projects on which the above individuals work, regardless of the source of funding for the project.

Definitions:

Research Documents/Records: Research records include but are not limited to case reports, study protocol and amendments, patient care data, objectives and purpose of the study, selection criteria, clinical procedures, Food and Drug Administration (FDA) records, serious adverse event reports, study design, and other documentation relating to study protocols. Research records do not include materials also maintained in the official patient medical record.

Data: Data is defined as recorded information, regardless of the form or medium on which it may be recorded, and includes writings, films, sound recordings, pictorial reproductions, drawings, designs, or other graphic representations, procedural manuals, forms, diagrams, workflow charts, equipment descriptions, data files, data processing or computer programs (software), statistical records, and other research data.

Research Financial Records: Research Financial Records include but are not limited to correspondence, purchasing records, scope of work, budgets, reports and service records.



II. PROCEDURE:

The sections below summarize the retention period, storage responsibilities, and disposal requirements of the different types of research records. At all times the research records shall remain the property of Children's unless otherwise specified by law, regulation or agreement.

A. Retention Period

1. Study site research records: The Children's study site research records for each project shall be retained for at least 10 years after termination of all research procedures. Children's, the study sponsor, and/or federal regulations may require longer retention of records for particular research. If the study documentation contains Protected Health Information (PHI) related to treatment that is not originated from the medical record, then the documentation/records shall be retained according to Policy 8.18 Document Retention and Destruction.
2. IRB research records: The IRB records for each study shall be retained for at least 3 years after termination of the IRB approval. Additional information regarding this requirement is located in Policy 1.16.
3. Research Financial Records: Research Patient Care billing records are retained 1 year after the study ends. Grants Accounting files are retained indefinitely.
4. Research Compliance Records: The Research Compliance Records shall be retained for 6 years from the date materials are replaced or updated.

B. Storage Responsibilities

1. Study site research records: The PI is responsible for the creation, collection, management, storage, and retention of research records. The PI may designate another study staff member to perform these tasks, but ultimately the responsibility and accountability reside with the PI. The study site research documents shall be maintained at the investigative site or appropriate Children's-approved storage facility. The PI shall provide access to research records to external sponsors of the research, designated governmental officials, and Children's representatives when such access is appropriate.
2. IRB research records: The IRB office is responsible for the creation, collection, management, storage and retention of research records. The IRB research documents shall be maintained in the IRB office or appropriate Children's-approved storage facility. The IRB shall provide access to research records to external sponsors of the research, designated governmental officials, and Children's representatives when such access is appropriate. See Policy 1.16 for further information regarding storage and access of IRB records.
3. Research Financial Records: The Office of Grant Accounting and Contracts is responsible for the creation, collection, management, storage and retention of research patient care billing records and grants accounting records. The Office of Grant Accounting and Contracts documents shall be maintained in the Office of Grant Accounting and Contracts office or appropriate Children's-approved



storage facility. The Office of Grant Accounting and Contracts shall provide access to research records to designated governmental officials and Children's representatives when such access is appropriate.

4. Research Compliance Records: The Research Compliance office is responsible for the creation, collection, management, storage, and retention of research compliance records. The Research Compliance documents shall be maintained in the Research Compliance office or appropriate Children's-approved storage facility. The Research Compliance Manager shall provide access to research compliance records to Children's representatives when such access is appropriate.

C. Disposal Requirements

1. This policy does not authorize or condone destruction of any research records in contemplation of or in anticipation of, or during, any audit, investigation or litigation. This prohibition of destruction is applicable regardless of whether the records are otherwise eligible for or past the point at which they may be destroyed.
2. Records meeting their retention requirement shall be reviewed for any holds that may exist, such as an audit. This is the responsibility of the individuals as outlined in Section B of this policy. For instance, it is the PI's responsibility to be aware of any holds involving research records under his/her care before authorizing the disposal of records.

III. REFERENCES:

21 CFR 312.62
21 CFR 812.140
21 CFR 312.57
Emory University



Policy Number:	10.14	Original Date Issued:	September 22, 2006
Section:	Compliance	Date Reviewed:	
Title:	Reporting Noncompliant Conduct in Research	Date Revised:	
Regulatory Agency:			

I. POLICY:

Employees of Children's who know or suspect that noncompliant conduct is occurring or has occurred in any research or sponsored program activities conducted and/or approved through Children's should report such conduct. No person shall be retaliated against by Children's or any of its employees for making a good-faith report of suspected noncompliant conduct in research or sponsored program activities.

Definitions:

Non-compliance: Any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with federal regulations or institutional policies governing such research. Non-compliance actions may range from minor to serious, be unintentional or willful, and may occur once or several times. The degree of non-compliance is evaluated on a case-by-case basis and will take into account such considerations as to what degree subjects were harmed or placed at an increased risk and willfulness of the non-compliance.

Examples include, but are not limited to:

1. Failure to obtain IRB approval;
2. Inadequate or non-existent procedures for the informed consent process;
3. Inadequate supervision;
4. Failure to follow Research policies and recommendations made by the IRB;
5. Failure to report adverse events or protocol changes;
6. Failure to provide ongoing progress reports; or
7. Protocol deviations;
8. Violation of Children's Standards of Conduct in carrying out research

II. PROCEDURE:

A. Reporting Noncompliant Conduct

Noncompliant conduct may be reported to the Research Compliance Manager, Children's Compliance Office or the Compliance Connection Line. Reports may be made via the Compliance Connection Line, or e-mail, telephone, interoffice mail,



personal contact or facsimile to the Research Compliance Manager or Children's Compliance Office.

Individuals who know or suspect that noncompliant conduct is occurring or has occurred should first discuss their concerns with their immediate supervisor, if appropriate. As necessary, concerned individuals should then contact the Research Compliance Manager, Children's Compliance Office or the Compliance Connection Line. Any research compliance concern may be reported anonymously through the Compliance Connection Line at 877-373-0126.

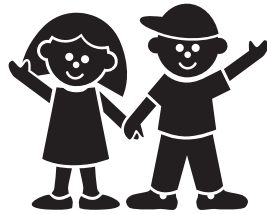
B. Confidentiality of Individuals Reporting Noncompliant Conduct

All reports regarding suspected noncompliant conduct will be maintained in a confidential manner. Persons who wish to remain anonymous may report concerns using the Compliance Connection Line.

Individuals receiving reports of noncompliant conduct will submit the information to the Research Compliance Manager or Children's Compliance Office for further action.

C. Investigating Reports of Noncompliant Conduct

The Research Compliance Manager will be primarily responsible for conducting or supervising the investigation, and will inform the Chief Compliance Officer of the investigation. The Chief Compliance Officer and the General Counsel will decide whether or not the General Counsel's office will oversee the investigation. If it is determined that the General Counsel's Office will not oversee the investigation, the Research Compliance Manager will proceed to investigate and initiate further action, if required, reporting final results to the Chief Compliance Officer. The Chief Compliance Officer, in consultation with the General Counsel's Office, will determine if any government or private funding agency must be notified prior to, during, or after any investigation. A summary of each complaint and resolution will be made to the Chief Compliance Officer, who will report all activities to the Operational Compliance Committee and the Audit and Compliance Committee quarterly.



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Some physicians and affiliated healthcare professionals who perform services at Children's Healthcare of Atlanta are independent providers and are not our employees.

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