IRB REFERNCE GUIDE

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Chapter 1 – INTRODUCTION

This handbook outlines the responsibilities of the Principal Investigator and should be read by the key personnel on the research team. We look forward to working with you to ensure the safeguarding of the rights, privacy and welfare of those who volunteer to participate in research studies.

I. MISSION STATEMENT

Children's Healthcare of Atlanta Mission Statement:

Children's mission is to enhance the lives of children through excellence in patient care, research and education.

II. PURPOSE OF AN IRB

Children's Healthcare of Atlanta Institutional Review Board (Children's IRB) is an ethical review board, whose purpose is to protect the rights and welfare of human subjects who participate in research. While the Principal Investigator is responsible for the conduct of the study, the IRB is responsible for determining that the proposed research is scientifically valid and that the anticipated benefits to the subjects as well as the knowledge that is expected to be gained outweigh the risks.

The IRB reviews and monitors research involving human subjects. It has the authority to approve, require modifications in which to approve, or disapprove research. The purpose of the IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in research. To accomplish this purpose, the IRB typically uses a group process to review research protocols and related materials. The IRB is responsible for approving what constitutes an adequate informed consent confirming that all necessary elements of informed consent are included. Children's IRB has a process for providing continuing education for both the Board members and Administrative Staff to ensure appropriate training in human research subject protections.

If you have any questions or concerns about the responsibilities of the Principal Investigator or for questions, comments, or suggestions regarding the review of research at Children's IRB, please contact us during normal business hours. You may reach us at (404) 785-7503, Monday through Friday. Please also visit the Children's IRB website at www.choa.org for forms, additional information, and links to other sites that will increase your knowledge and understanding of the research process. The IRB is available as a resource to assist investigators in any matters that involve research participants (e.g., complaints, concerns).

III. REGULATIONS AND DEFINITIONS GOVERNING THE IRB

Children's IRB operates in compliance with:
- Protection of Human Subjects (DHHS), 45 CFR 46
- FDA Regulations on Human Subjects Research, 21 CFR 50, 56, 312, 812
- Standards for Privacy of Individually Identifiable Health Information, 45 CFR 160, 164
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Children's IRB follows the definitions of Human Subject and Research outlined by the Protection of Human Subjects (DHHS), 45 CFR 46 and by the FDA, 21 CFR 50 & 56.

A. Definition of Human Subject

45 CFR 46.102(f) defines a human subject as an individual about whom an investigator conducting research obtains data through intervention or interaction with individual or identifiable private information.

21 CFR 50.3(g) and 56 CFR 102(e) define a human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

Intervention or Interaction includes physical procedures performed on an individual, manipulation, communication or interpersonal contact with an individual or manipulation of an individual's environment.

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

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

Coded: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

De-Identified: Information that has certain identifiers (see Identifiers below) removed in accordance with 45 CFR 164.514; no longer considered to be identifiable. It is important to note that voice recordings are considered identifiers. If you plan to audio record interviews for transcription, even if you plan to destroy the source, these recordings are considered identifiable.

Identifiers: Under the HIPAA Privacy Rule "identifiers" include the following:

1. Names
2. Geographic subdivisions smaller than a state (except the first three digits of a zip code if the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people and the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000).

3. All elements of dates (except year) for dates directly related to an individual, including birth date,admission date, discharge date, and date of death and all ages over 89 and all elements of dates (including year) indicative of such age (except that such ages and elements may be aggregated into a single category of age 90 or older)
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code (excluding a random identifier code for the subject that is not related to or derived from any existing identifier).

B. Definition of Research

45 CFR 46.102(d) defines research as a systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge.

21 CFR 50.3(c) and 21 CFR 56.102(c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous for purposes of this part.

IV. IRB AUTHORIZATION AGREEMENTS

The Children's Institutional Review Board (IRB) is generally the responsible entity for reviewing research involving human subjects conducted by Children's investigators. However, in cases where use of an external (non-Children's) IRB is

appropriate (e.g., in multi-site studies where all sites are using the same IRB; or in cases where review at another IRB is required and duplicate review by the Children's IRB would add unnecessary administrative burden on the investigator), the Children's IRB may defer to the external IRB under what is known as an "IRB Authorization Agreement" (IAA), pursuant to guidance from the DHHS Office for Human Research Protections (OHRP), at http://www.hhs.gov/ohrp/IRBfaq.html.

Currently Children's IRB has IRB Authorization Agreements in place with the Emory University, Georgia State University, Georgia Institute of Technology, and the Morehouse School of Medicine IRBs. These agreements stipulate the IRB of record and vary in their language. The Emory University agreement is based on the employer of the investigator (Children's vs. Emory) and whether Children's Healthcare of Atlanta medical records are involved. The Morehouse School of Medicine agreement is based upon the population involved in the research study (child vs. adult). The Georgia Tech and Georgia State agreements are based on where the majority of the research activities take place. If you feel that an IAA is needed in the case of your project(s), please contact the Children's IRB office for guidance.

Chapter 2 – THE BELMONT REPORT (Ethical Principals and Guidelines for the Protection of Human Subjects of Research):

The Belmont Report is the cornerstone statement of the ethical principles upon which the Federal Regulations for protection of human subjects are based. Children's IRB recommends that all Principal Investigators and key research personnel read the Belmont Report.

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three quintessential requirements for the ethical conduct of research involving human subjects.

Respect for persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Justice requires that the benefits and burdens of research be distributed fairly.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles.

The Belmont Report: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

Chapter 3 – Categories of Research Review

I. Full Board Review:

Full Board Review: Reviewed by a quorum of Board members.

Human subject research studies that are not classified as exempt or expedited require review by the full IRB at a convened meeting. Children's IRB meetings are typically held once a month, on the fourth Thursday of each month, but may be cancelled by the Administrator for insufficient applications, holidays, or inability to secure a quorum.

Children's IRB uses a primary reviewer system for full Board reviews. Submission application materials are typically sent to the Board at least 10 days prior to a meeting. When a primary reviewer is used, he/she leads the discussion of each project they reviewed and the Board determines whether the project meets the criteria for approval and whether revisions to the protocol or informed consent are needed.

The informed consent is reviewed for accuracy, clarity, and inclusion of the required elements of consent. By a majority of those present at the meeting, each study is either: (1) approved as submitted; (2) approved pending modifications requested by the Board and then reviewed by an expedited reviewer after receipt of additional information or revisions; (3) deferred, pending review at a subsequent Board meeting after receipt of significant additional information or revisions; (4) tabled pending review at a subsequent board (studies may be tabled due to a loss of quorum, inadequate information, or other administrative issues); or (5) disapproved. Approval documents will usually be mailed within 3 business days of the determination.

II. Expedited Review:

Federal regulations recognize that certain aspects of research may be reviewed by an IRB through an expedited review procedure (45 CFR 46.110) (21 CFR 56.110). Children's IRB employs the expedited review procedure for minor changes in previously approved research during the period (of one year or less) for which approval is authorized and for research that meets the expedited review category requirements at initial submission or continuing review.

Expedited review means that the IRB Chairman or designee is solely responsible for the review and approval. Expedited review decision documents will usually be sent within 3-5 business days. The Board will be apprised of research items approved by expedited review.

III. Exempt Human Subject Research:

Certain types of human subject research that present little or no risk to the participants may be classified as exempt from the federal regulations (45 CFR 46.101(b)) (21 CFR 56.104). The Chairman or designee will determine whether the research meets the exempt criteria, based on review of the correspondence concerning the request, protocol, and associated documents. The decision will usually be communicated to the Principal Investigator within 48 hours of the determination being made.

Chapter 4 – PRINCIPAL INVESTIGATOR RESPONSIBILITIES

I. Study Conduct:

The Principal Investigator is responsible for the ethical conduct of the research study, and for protecting the health and welfare of all subjects enrolled at his/her site(s). The clinical research study must be conducted as stated in the protocol and in accordance with all applicable federal, state and local laws and Good Clinical Practices (GCP). It is expected that the investigator have the resources necessary to protect human participants, including sufficient time to conduct and complete the research, as well as access to a population that will allow recruitment of the necessary number of participants.

The Principal Investigator is responsible for knowing and following the IRB-approved protocol. The investigator should be familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current investigator's brochure, in the product information and in other information sources provided by the sponsor. Furthermore, it is expected that the investigator follow the study's randomization procedures, if any, and that they ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding. The Principal Investigator agrees to abide by the Principal Investigator's Assurance as stated in the Initial Submission Application for the Investigator.

II. Training and Education / Investigator and Study Staff Qualifications:

The Principal Investigator and all research personnel should have appropriate training in conducting clinical trials and each should be aware of the obligations to communicate with the IRB during the study. The Principal Investigator and all research personnel are required to complete the CITI and GCP modules designated by Children's prior to conducting research and must renew the CITI and GCP every two years. *Children's Policy 1.74 – Investigator Qualifications*

While the Principal Investigator is ultimately responsible for the conduct of the research study, the PI may delegate research responsibility to appropriately qualified persons. However, they must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. Further, the PI is responsible for maintaining a list of appropriately qualified persons to whom they have delegated significant study-related duties.

III. Record Keeping:

The study records need to be kept in accordance with *Children's Policy 1.68 Regulatory Binders for Clinical Research* and *Policy 8.47 Research Record Storage, Retention and Disposition of Documents/Records*, as directed by the Sponsor and as required by applicable law and/or regulation. The Principal Investigator is responsible to maintain complete and accurate records.

IV. Audits and Inspections:

All records of human subject research are subject to inspection by the Children's IRB, Office of Research Compliance, regulatory agencies and the sponsor.

Children's Office of Research Compliance Office also has the authority to conduct audits of investigative sites under its review. Human Subjects Research selected for quality assurance reviews will focus on, but are not limited to active studies with moderate to high risk to participants, investigator-initiated protocols, research with potential for conflict of interest, and or "for cause" interests of the IRB or Compliance Office.

Audits may be one of three types: 1) Not for cause, scheduled or unscheduled, 2) Informed consent review, or 3) For cause. Audit review summaries are provided to the IRB, the Principal Investigator and the Director of Clinical Research. Quarterly reports are provided to the Audit and Compliance Committee.

Children's Office of Research Compliance or an independent third party may observe the implementation and conduct of human subject research activity under the IRB's review, including observance of the informed consent process, at any time.

The Principal Investigator is responsible for being prepared at all times for an audit or inspection.

V. Form FDA 1572:

The Principal Investigator is responsible for completing and submitting the Form FDA 1572 prior to the start of the study, if applicable. This is a contract between the Principal Investigator and the FDA which outlines the responsibilities that the Principal Investigator agrees to assume in order to conduct the study. All copies of the original and revisions to the Form FDA 1572 need to be forwarded to Children's IRB. Additional information can be found on the FDA website:

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

VI. Referral Fees, Incentives, and Bonus Payments for Recruitment:

Referral Fees: Children's IRB does not support the recruitment of research subjects by payment for referrals to research subjects or other persons including, but not limited to, the Principal Investigator, Sub-Investigator or Clinical Coordinator(s) for research under its review. This is in accordance with the American Medical Association (AMA) Code of Medical Ethics which states, "Offering or accepting payment for referring patients to research studies (finder's fees) is also unethical." *Children's Policy 1.77 – Recruitment of Subjects*

Incentives and Bonus Payments for Recruitment: The Principal Investigator should report to Children's IRB any proposed incentives, gifts, or bonus payments to the Principal Investigator or study staff other than the original contractual agreement for

review. These will be reviewed on a case by case basis. Children's IRB is concerned that these practices may cause undue influence on the research staff.

VII. Summary of Requirements of the Principal Investigator:

The Principal Investigator is required to provide the following information and reports to Children's IRB. These requirements should be reviewed by all individuals involved in the research activities. If you have any questions, please call Children's Healthcare of Atlanta Institutional Review Board at 404-785-7477 and a member of our staff will be glad to assist you.

Amendments: Once a study has received initial IRB approval, any change to the study is considered an amendment. All amendments must be submitted to Children's IRB for review and approval prior to implementation, unless to eliminate immediate hazards to subjects, in which case the IRB must be notified immediately.

Advertisements and Recruitment Material: These items are reviewed in accordance with FDA and DHHS guidelines, and must be approved by Children's IRB prior to use. Once an Investigator has received initial IRB approval, any advertisements and recruitment materials submitted for approval thereafter are considered amendments and must be accompanied by a completed Request for Modification Form.

Revisions to 1572: Revisions to the FDA 1572 Form must be submitted to Children's IRB. If the revised 1572 is due to a change of site/additional site, the revised FDA 1572 must be accompanied by a completed Request for Modification Form requesting to add or change a site

Serious Adverse Event: Children's IRB requires that the Serious Adverse Event Report be submitted if the event is unexpected, serious and related or possibly related to the research. A *serious* event is one which occurs to a subject while participating in the study that: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; is a congenital anomaly/birth defect; results in persistent or significant disability/incapacity; requires intervention to prevent one of the aforementioned outcomes; or should be (in the Investigator's opinion) considered by the IRB. Note: questions regarding whether an event is considered an SAE can often be resolved by referring to the description of an SAE in the Protocol or consulting with the Sponsor. An *unexpected* event is an event, the nature or severity of which is not consistent with the potential risks in the Informed Consent Document(s), Protocol, Investigator's Brochure (IB), or Investigation Plan. The serious unexpected event should be reported **within 10 business days** of the Investigator's knowledge of the event. All fatal or life threatening events that are related or possibly related to the research should be reported to Children's IRB immediately. Serious Adverse Events that are not related to the research do not need to be reported.

Significant Protocol Deviation: Children's IRB requires that all significant protocol deviations are to be reported **within 10 business days** of when the site becomes aware of

the study event. Children's IRB defines significant deviations as those that: (1) affect the scientific design/integrity of the study; (2) affect the rights, safety, or welfare of study subjects; (3) change the risk/benefit ratio; or (4) violate an ethical principle. Non-significant deviations do not need to be reported to the IRB immediately unless the Sponsor/site SOPs require the Investigator to do so. All non-significant deviations should be submitted at study renewal and maintained in the regulatory binder.

Unanticipated Problems (Other): There may be other unanticipated problems (that do not fall within the classifications for SAEs, External SAEs or Significant Protocol Deviations) but which: (1) involve risk(s) to the research subject(s) or others; (2) affect the rights, safety or welfare of study subjects; (3) affect the scientific design/integrity of the study; (4) change the risk/benefit ratio; or (5) violate an ethical principle. Unanticipated Problems may include problems that affect privacy (e.g., an unauthorized person gaining access to confidential study records), or safety (e.g., the disappearance of study medication). All Unanticipated Problems should be reported **within 10 business days** of the site becoming aware of the problem.

Sponsor-Granted Exceptions: Children's IRB requires that all Sponsor-granted protocol exceptions that may affect the scientific design/integrity of the study, affect the rights, safety or welfare of study subjects, or change the risk/benefit ratio, must be reported to the IRB for IRB approval *prior to implementation*, except where necessary to eliminate apparent immediate hazard to human subject(s). Exceptions must be submitted to the IRB accompanied by documentation of the Sponsor's approval thereof. Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)]. Exceptions necessary to eliminate apparent immediate hazard to human subjects should be reported promptly after initiation.

Continuing Review: An Investigator must receive continuing review approval prior to the "study expiration date" listed on the initial or renewal approval documents. The Investigator should submit the Continuing Review Form and all necessary documents not less than one month prior to the last Children's IRB meeting preceding the expiration date.

Federal regulations do not allow the IRB to grant extensions or grace periods, so timely submission of the Continuing Review Form and documents is important to avoid unnecessary interruptions in the study.

All reports minimally include the current study status, the number of subjects consented and their status, a current risk-benefit assessment based on study results, audit and monitoring report information, change in community attitudes, and any new information since the IRB's last review.

A reminder will typically be sent 60 AND 30 days prior to the due date, but it is primarily the Principal Investigator's responsibility to ensure that all required

continuing review reports are submitted to the IRB early enough to allow time for the appropriate level of review.

Investigator Noncompliance: The Investigator and study staff must report noncompliance with the study protocol and procedures, and/or rules and regulations governing research (i.e. state and federal regulations, IRB policies and procedures, etc.) to the IRB or to Research Compliance. The IRB and Research Compliance will review the reported concern and will determine whether instances of noncompliance constitute serious or continuing noncompliance. The IRB will report any instance of an Investigator's serious or continuing noncompliance with the requirements of the FDA, OHRP and AAHRPP (and other agencies, if applicable) and/or IRB, as set forth in the Federal Regulations and/or Children's IRB Policies and Procedures, by notice to the Investigator, Sponsor and the regulatory agency.

Investigator to Withdraw from Study: Notification of the Investigator's decision not to conduct the study or to withdraw from the conduct of the study must be submitted to the IRB. A Close-Out Report Form will need to be submitted unless a new Investigator has been approved to continue with the study site.

Termination or Close-out of a Study: After the last subject has completed the study and the Sponsor/CRO (if applicable) has indicated that the study is completed at the site, the Close-Out Report Form must be submitted to ensure proper closeout. This report should include the date that the final subject completed the study. A Close-Out Report should also be submitted in the event of cancellation or termination of a study by the PI, the Sponsor's termination or suspension of a clinical study, or withdrawal of approval from another IRB.

Study Closeout: A study may be closed when all research activities involving human subjects, including data analysis with individually identifiable or coded private information are complete.

Chapter 5 – SUBMISSIONS TO THE IRB

I. New Study Submissions:

Principal Investigators are required to submit the Initial Submission Application for the Investigator/Site and all other required documents. All forms and guides are located on the Children's IRB website and should be completed electronically.

II. Change in Principal Investigator, Sub-Investigator(s) and study staff:

When there is a change of Principal Investigator for an already approved study, the following is required to be submitted to Children's IRB for review of the new Principal Investigator:

- Request for Modification form for change of study staff
- Signatures of the outgoing Principal Investigator as well as the new PI are required
- Revised study documents with updated Investigator, Sub-Iinvestigor and study staff name(s) and information (i.e. protocol, consents, advertisements, etc.)
- Copy of the revised Form FDA 1572, if applicable

III. Change in Site or Adding Additional Sites:

When there is a change in site location or additional sites are added, the following is required to be submitted to the IRB:

- Request for Modification for each site that has changed or been added to the study
- Revised study documents with updated site information
- Copy of the revised Form FDA 1572, if applicable

IV. Translations for Subject Information and Informed Consent:

Informed consent must be presented in a language understandable to the subject. If the subject does not speak English, Children's IRB requires a certified translation of the IRB approved informed consent. Some Sponsors require back translations for accuracy. All revisions of the informed consent must go through the certified translation process; however Children's IRB may make minor changes without going through the certification process.

Children's Investigators can arrange to have the informed consent and any other study related document translated into any language through the Translations Department. As an alternative, the site or study Sponsor can submit a document that has already been translated along with a certification statement for verification to Children's IRB.

Short Form:

When can the short form be used?

- The participant or LAR does not speak/understand English; AND
- The participant or LAR speaks only a language(s) that was not anticipated in the study population or location; AND

- An approved translated consent form in participant's language has not been approved by the IRB; AND
- There is not adequate time for preparation and IRB review and approval of a translated consent form

How must the short form be used?

- An oral translation of the approved English language consent form should be presented in a language understood by the prospective participant.
- There must be a translator. Children's IRB custom is to encourage the use of professional or certified translators as we do for written translations. Exceptions may be made, however, on a case-by-case basis depending on availability of professionals.
- There must be a witness to the oral presentation. The witness must be fluent in both English and the language of the presentation. The translator may also serve as the witness.
- The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form have already been approved by the convened IRB. If the foreign language version cannot be written by a certified or professional translator, the researchers must also submit an English back-translation of the short form. Many translated short forms are available on the Children's IRB website. Forms provided by Children's do not require back-translation.
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What signatures are required?

- The participant signs and dates the short form (receives a copy of the signed short form and a written summary of what is to be said to the participant). For cases in which a short form is being used, the English language informed consent document may serve as this written summary. The Children's IRB, however, reserves the right to require the PI to provide the protocol translated into the participant's primary language.
- The study staff obtaining consent signs and dates a copy of the written summary (and any additional documentation that is required by the IRB). The study staff receives a signed copy of the short form and written summary.
- The witness signs the short form and the summary.
- The translator signs nothing unless serving as the witness too.

What has to be given to the IRB?

- The IRB must receive all foreign language versions of the short form and written summary.

What the Federal Regulations have to say about the short form:

> (2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.
>
> Guidance can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/ic-non-e.htm

V. Advertisements and Recruitment Materials:

Advertisements and recruitment materials may be submitted to Children's IRB for review by regular mail, fax, or e-mail. Advertisements and recruitment materials submitted for review after the Investigator has received initial approval are considered amendments and must be accompanied by a completed Request for Modification form.

Advertising or recruiting for study subjects is considered to be the start of the informed consent process. **The information contained in the advertisement/recruitment materials and the mode of communication must be reviewed by the IRB and approved before they are used.** All submitted materials must comply with applicable federal regulations, and state and local laws. Furthermore, it is Children's IRB's expectation that the recruitment processes which are employed by the Principal Investigator and the research staff are fair and equitable.

Children's IRB requirements for advertisements and recruitment materials:

- Purpose of research is stated
- Does not state or imply a certainty of favorable outcome beyond what is outlined in the consent document and the protocol
- Statement that the information provided pertains to a research study
- Contact information should be included
- Must not be coercive
- Compensation must not be emphasized (e.g., by such means as larger or bold type)
- Compensation explained if greater than $1000
- Does not allow compensation for participation in a trial to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing (FDA-regulated research)
- Must not include testimonials (defined as a statement in support of a particular truth, fact, or claim). Recruitment materials cannot contain statements that explicitly or implicitly make effectiveness claims about the investigational product or procedure. Testimonials, in general, advertise the product or procedure that they discuss in the words of a "satisfied user," and so, by their very nature, are claiming success, improvement, and/or effectiveness. Should not use the terms: "state of the art," "cutting edge," "breaking technology," or "improved."
- Does not make claims, explicitly or implicitly, that the test article is known to be equivalent/superior to any other drug, biologic, or device
- Does not make claims, explicitly or implicitly, that the test article is safe/effective for the purpose under investigation
- Benefits are included but not guaranteed
- Must not use the word "free" when referring to procedures and medications that may be received as a part of participation in the research study. Acceptable language would be, "at no cost," or "at no charge."
- Does not contain the word "new" when referencing the test article, unless qualified as investigational

- The word “earn” should not be used
- Must define the word “placebo” (if used)
- For pediatric studies, advertisements should be directed at adults
- Does not include coercive language, tone, or exculpatory language

For print advertisements, please submit a copy of the print ad in the format that it will appear, so that Children’s IRB can review the layout of the advertisement as well as the text. If you are submitting advertisement recruitment materials with a reference or link to a website, any research-related content, including any information which pertains to a study under the review of Children’s IRB, must be submitted to the IRB for review and approval prior to use. It is your responsibility to ensure that your submission includes any web content which requires IRB review.

Children’s IRB does not require the submission of, but will review upon request, website recruitment content where the system format limits the material presented to basic trial information, such as the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and information on how to contact the site for further information. Examples of such listings include content posted to government-sponsored sites, such as the National Institutes of Health (NIH) ClinicalTrials.gov website, the NIH National Cancer Institute’s cancer clinical trials listing (PDQ), and the AIDS Clinical Trials Information Service (ACTIS). However, Children’s IRB does require the submission of web content where the opportunity to add additional descriptive information is not prevented by the system format, for review and approval prior to use.

It is your responsibility to ensure that links to external sites, which are contained within web submissions, are in compliance with applicable regulations and IRB requirements, as Children’s IRB does not review this material.

Radio and television advertisement scripts must be submitted to Children’s IRB for approval. It is recommended that scripts are reviewed and approved prior to production of CDs/MP3s for radio and DVDs for television ads. All recruitment media (CDs/MP3s for radio and DVDs for television) must be approved before advertising begins.

Recruitment materials/advertisements provided with the **original submission** will be reviewed with initial review. Children’s IRB will notify you if any revisions are required before approval can be granted.

Recruitment materials/advertisements submitted **after the Investigator’s initial approval,** must be accompanied by a completed Request for Modification Form. These items usually will be reviewed by expedited review within 3 business days. Children’s IRB will notify the Principal Investigator or designee if any revisions are required before approval can be granted.

Children’s IRB must review any revision made to previously approved recruitment materials/advertisements. These include text changes, and other image changes such as

pictures, font type or size. Please contact Children's IRB if there are any questions regarding changes to participant recruitment materials/advertisements.

VI. Telephone Screenings:

Children's IRB requires that a telephone screening script include the following information:

- The prospective subject must provide their permission for the screening to proceed and for the screener to collect confidential medical information (otherwise, the call should be ended)
- The prospective subject will be told that the information gathered from the screening procedure will be kept confidential
- The prospective subject will be told what will happen to the information collected (i.e. stored in a database)
- The prospective subject will be told what will be done with the information if he/she does not qualify for this study (i.e. will the information be destroyed, or, with the permission of the prospective subject, will the information be kept in a database and used for another study. In the later case, the prospective subject **must give** his/her permission for the information to be stored)
- The prospective subject must be told that he/she does not have to answer any questions they do not want to respond to, and may choose to end the phone call at any time

A telephone consent template can be found on the Clinical Research web page under Institutional Review Board, Forms and Instructions.

Note: See Chapter 8 Informed Consent; Informed Consent Requirements When Determining Eligibility for Research, for additional information.

HIPAA RESPONSIBILITIES: This is applicable to covered entities as defined in the Privacy Rule.

If Protected Health Information (PHI) is to be recorded into a database, the Principal Investigator will need to complete and submit a HIPAA Waiver of Authorization. See the Children's IRB website for the form. The completed Application should be submitted along with the telephone screening script for approval.

VII. Amendments to Previously Approved Research:

Any change to previously approved research must be reviewed and approved by the IRB prior to implementation, except changes made to eliminate immediate safety hazards to participants, which must be immediately reported to the IRB. For all changes submit any revised documents with a Modification form.

A. **Protocol Amendments** – Submit a completed Request for Modification Form and a cover letter detailing the request, if necessary, along with the following attachments:

- Copy of Protocol
- Copy of informed consent detailing proposed changes, if any
- Copy of 'Summary of Changes' or tracked version of protocol showing changes
- For device studies, a copy of the FDA IDE letter approving the amendment, if applicable
- For drug studies, a copy of the FDA IND letter, if applicable
- Copy of questionnaires or surveys to be used with the study, if changed
- Copy of advertisements/recruitment materials, if changed

Protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the subjects. The IRB should be notified of this occurrence immediately.

B. **Revisions to the Informed Consent Document** – Submit a completed Request for Modification Form and a cover letter detailing the request These should be submitted with changes clearly marked by red lining, highlighting, or tracking the already approved document **and a clean copy of** the proposed revised document. Consent revisions will be reviewed by the full Board unless the changes meet Children's IRB's requirements for expedited review.

Any IRB approval of a revised informed consent document that might relate to the subjects' willingness to continue participation in the study will necessitate the re-consent of all current subjects (active or follow-up) in the study. Subjects who have completed the study and those in follow-up may be mailed a copy of the changes to the consent document. The FDA and Children's IRB do not require the re-consenting of subjects that have completed their active participation unless information that has been received affects the risks to research subjects that have already completed the study.

C. **Changes to the Investigator's Brochure**: The Sponsor may update the Investigator's Brochure (IB) during the course of the study. Changes to the Investigator's Brochure should be submitted to the IRB. Documentation of IRB review of the IB will be provided.

D. **Change in Principal Investigator**: During the course of a study, the Principal Investigator may change. This change must be approved by the IRB prior to implementation.

E. **Addition or Change in Study Site**: During the course of a study it might be necessary to close or add sites. This change must be submitted to the IRB for review and approval.

F. **Recruitment, Screening Scripts, or other study materials not submitted prior to the initial approval of a study**: All materials that will be used as part of a study must be reviewed and approved by the IRB prior to use. These materials can be submitted as part of the initial study protocol; however, many times these materials are not available at the time of the initial submission. Materials which are submitted following initial approval of a study must be submitted as an amendment.

VIII. Forms:

Children's IRB Forms are located on our website at. https://www.choa.org/research/institutional-review-board/forms. Children's offers several ways to submit the completed submission documents. Once you complete the forms online, save, print and all forms have the appropriate authorized signature they can be delivered to our office, mailed, faxed or emailed. For applications submitted via email, the signature page should be either scanned and emailed or faxed. The IRB will accept electronic signatures.

IX. Criteria for IRB Approval of Research:

Only those research submissions which (at least) satisfy the criteria for IRB approval of research as outlined in 21 C.F.R. 56.111 and/or 45 C.F.R. 46.111 (as applicable) will be approved by the IRB. These criteria are as follows:

A. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

B. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

C. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

D. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by regulation.

E. Informed consent will be appropriately documented, in accordance with and to the extent required by regulation.

F. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

G. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

X. Notification of Approvals and Acknowledgements: All determinations and notifications are usually sent to the PI within three (3) business days

Chapter 6 – CONTINUING REVIEW

Continuing review of IRB approved research is required under 45 CFR 46.109(e) and/or 21 CFR 56.109 (f). The period for continuing review is determined by the IRB; however, it must occur at least annually.

The Continuing Review form requires information about the number and status of subjects involved in the study and a progress report for the research.

The Continuing Review form is located on the Children's IRB website.

I. Continuing Review Form: (Application for Continuation)
Children's IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. All non-exempt research projects will receive Full Board or Expedited continuing review depending on whether they qualify for expedited review; however the Board is notified of all Expedited Reviews at the next committee meeting as required by regulations. It is the responsibility of the IRB to perform a substantive continuing review and consider the same issues as during initial review.

It is the Principal Investigator's responsibility to submit the Continuing Review in sufficient time to permit review and approval prior to the study expiration date. **The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval.** Continuing review and reapproval of research must occur on or before the one year anniversary of the initial IRB approval date. To assist in this Principal Investigator obligation, Children's IRB will typically send reminder notices via email at 60 and 30 days prior to expiration of the study. **It is important to remember that the IRB needs to receive the Continuing Review Report in sufficient time for review and re-approval of the research prior to the study expiration date. It is recommended that the Continuing Review Reports be submitted not less than 30 days prior to the study expiration date.**

If the Principal Investigator does not submit the Continuing Review in time for Children's IRB review prior to the expiration date, he/she will be notified by letter that the IRB approval has lapsed and the study has expired. This letter details that all recruitment and study related activities (advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information), including data analysis, **must stop**. One exception would be if the cessation of treatment poses a threat to the life or welfare of a subject. If continuation of research procedures is necessary for subject safety, the IRB must be notified **immediately**.

The PI will have 90 days to reinstate the study to an active status. If he/she does not submit within 90 days after the lapse in approval, the study will be closed permanently and the PI will have to submit as a new study. Failure to submit for renewal may result in Board action(s) including, but not limited to, suspension and/or termination of IRB approval or a finding of serious and/or continuing noncompliance.

Children's IRB will send continuing review approval documentation to the study site which includes the study expiration date as well as the due dates for the Continuing Review reports. Continuing Review forms are available on the Children's IRB website.

II. Progress Report/Study Update:

The Progress Report/Study Update must be submitted with the Continuing Review to detail the progress that has happened with the study since the last IRB submission for review.

It is the Principal Investigator's responsibility to submit a Progress Report/Study Update with the Continuing Review documents. Please note, failure to submit a Progress Report/Study Update (if required for the study) may result in an incomplete submission and delay review.

III. Study Closure/Final Report:

When all research activities involving human subjects, including follow-up visits and data analysis with individually identifiable data and the Sponsor/CRO (if applicable) has indicated that the study is completed at the site, the Principal Investigator must submit a Close-Out Report form to the IRB to ensure proper closeout. This report should include the date that the final subject completed the study. This report must also be submitted when/if the study is cancelled or terminated. Furthermore, it is the responsibility of the investigator to also inform the regulatory authority with any reports which are required.

Following review, an acknowledgement will be sent to the investigator/site.

Chapter 7 – REPORTABLE EVENTS

Many types of events must be reported to the IRB. In general, events that are unanticipated and increase the risk to subjects or others, which may significantly affect the conduct of the clinical trial, which could affect a participant's willingness to continue in the study, or could be noncompliance, must be reported to the IRB. It is the IRB's responsibility to determine whether or not an event is an unanticipated problem involving risk to subjects or others and to notify the investigator of what steps, if any, are necessary to continue the study. *Children's Policy 1.59 – Research Adverse Events and Unanticipated Problem Reporting*

Unanticipated Problems Involving Risk to Subjects or Others are considered, in general, to include any incident, experience, or outcome that meets the following criteria:

1. Unexpected: (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related: to participation in the research (*possibly related* means that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study product or procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

I. Protocol Deviations:

Protocol deviations are study events where the Children's IRB-approved research protocol has not been followed. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected harm to subjects.

The Principal Investigator is responsible for reporting all significant deviations to the IRB; however data collection and communication of such events may be delegated to appropriate clinical site research personnel.

All significant protocol deviations should be reported within 10 business days of when the site becomes aware of the study event, using the Event Reporting Form available on the Children's IRB website.

The Principal Investigator must sign the Event Reporting Form prior to submission to Children's IRB.

DEFINITIONS:
Deviation: A substantive unintentional change to the protocol or procedures involving risks or with the potential to recur that adversely affected the rights, welfare, or safety of subjects; the integrity of the research; or the subject's willingness to continue.

Examples of Significant Deviations:

- A subject refuses protocol specific procedures.
- Study drug not returned by subject
- Study materials stolen (i.e. study drug, laptop containing study-related information)

Sponsor monitors often request that the site send the entire Protocol Deviation/Violation Log. Children's requires submission of only significant deviations using the above criteria. Significant deviations should be submitted on the Event Reporting Form that can be found on the Children's IRB website (with supporting documentation as applicable).

All Significant Protocol Deviations will be reviewed and acknowledged. Deviations determined to be non-compliance will be reviewed by the Research Compliance Manager and referred for a determination of serious or continuing non-compliance.

II. Serious Adverse Events (SAEs):

DEFINITIONS:
Serious Adverse Event: An incident which occurs to a subject while participating in the study that: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; is a congenital anomaly/birth defect; results in persistent or significant disability/incapacity; requires intervention to prevent one of the aforementioned outcomes; or should be (in the investigator's opinion) considered by the IRB.

Note: Questions regarding whether an event is considered an SAE can often be resolved by referring to the description of an SAE in the protocol or consulting with the Sponsor.

Unexpected: An event, the nature or severity of which is not consistent with the potential risks in the Informed Consent Document(s), Protocol, Investigator's Brochure (IB), or Investigational Plan.

The Principal Investigator is responsible for reporting unexpected Serious Adverse Events (SAEs) to Sponsors and Children's IRB; however, he/she may delegate the data collection and communication of such events to appropriate clinical site research personnel.

The Principal Investigator must sign the completed Event Reporting form prior to submission to the IRB.

Children's IRB requires that all unexpected Serious Adverse Events (SAEs) be submitted within 10 business days of the investigator's knowledge of the event. All fatal or life threatening events should be reported immediately to Children's IRB. All unexpected Serious Adverse Events (SAEs), including fatal or life threatening events should be immediately reported to the Sponsor.

Follow-up Reports: For all initial SAE reports that do not show resolution, Children's IRB requests a follow-up report with additional information, including date resolved. More than one follow-up report may be sent to the IRB with information as it becomes available.

For unexpected serious adverse drug reactions, the Principal Investigator is responsible for following regulatory requirements related to the reporting of such events to the regulatory authority and the IRB.

For reported deaths, the Principal Investigator or designee should supply the Sponsor and IRB with any additional requested information (e.g., hospital records and autopsy reports).

Upon receipt and review of an SAE, Children's IRB may request additional information from the Principal Investigator. If Children's IRB determines, after review of an SAE that additional information should be provided to the subjects, a request will be made to the Sponsor and Principal Investigator for a revision or addendum to the informed consent.

All Serious Adverse Events will be reviewed and acknowledged.

III. Unanticipated Problems (Other):

"Other" Unanticipated Problems include any unanticipated problem that does not fall within the classifications for Serious Adverse Events, External Serious Adverse Events, or Significant Protocol Deviations, but which: involves risk(s) to the research subject(s) or others; affects the rights, safety or welfare of study subjects; affects the scientific design/integrity of the study, changes the risk/benefit ratio; or violates an ethical principle.

The Principal Investigator is responsible for reporting Unanticipated Problems to trial Sponsors and Children's IRB; however, he/she may delegate the data collection and communication of such events to appropriate clinical site research personnel.

The Principal Investigator must sign the Event ReportingForm prior to its submission to Children's IRB.

All unanticipated problems involving risk to subjects or others should be reported to Children's IRB within 10 business days of the site becoming aware of the problem.

Examples of unanticipated problems involving risks may include, but are not limited to the following:

- Unexpected frequency or severity of expected adverse events
- Incarceration of a study subject
- New findings that may influence a subject's willingness to continue participation in the study
- Subject complaints
- Breach of confidentiality or privacy
- Unauthorized use or disclosure of Protected Health Information (PHI)
- Study drug or test article accountability discrepancies
- Adverse results from a Data Safety Monitoring Committee/Board (DSMC/B)
- Unanticipated legal risk to a subject
- Unanticipated additional costs to subjects

All Unanticipated Problems will be reviewed and acknowledged.

IV. External Adverse Events (IND Safety Reports*):

External adverse events involve study participants who are not enrolled at a study site approved by Children's IRB or where the Principal Investigator (PI) is not under the oversight of Children's IRB. The Principal Investigator typically receives notification of these external events from the Sponsor in the form of an IND Safety Report.

***** *The term "IND Safety Report" is used here to represent all types of external adverse events reports, including, but not limited to, IND Safety Reports, MedWatch Reports, Data Safety Monitoring Board Reports, and FDA Safety Alert Letters.*

IND Safety Reports should be submitted to Children's IRB only if, in the opinion of the Sponsor/CRO/SMO or Principal Investigator, the report meets **at least one** of the following conditions:

1. Information on the report affects the rights, safety, or welfare of all participants in the study.
2. The report is for a device study.
3. The report is being submitted per Sponsor or Site requirements.

For single-site and multi-site studies, it is the Principal Investigator's responsibility to submit all IND Safety Reports that meet one of the submittal conditions listed above.

All IND Safety Reports concerning other sites that meet one of the submittal conditions above should be submitted to Children's IRB within 10 business days of receipt.

Data Safety Monitoring Board reports and Sponsor monitoring reports should be submitted to the IRB. Iif no safety issues are noted in the report, the DSMB report can be submitted at the next renewal. If there is a safety issue, the DSMB report should be submitted immediately.

V. Sponsor-Granted Exceptions:

DEFINITION:
Exception: A protocol exception is a type of planned change to the Children's IRB-approved research protocol that (unlike an amendment) does not result in a permanent revision to the research protocol. A protocol exception typically involves a single subject or, less commonly, a small group of subjects.

Protocol exceptions are planned changes from the Children's IRB-approved research protocol that (unlike amendments) do not result in permanent revision to the research protocol.

The Sponsor and Principal Investigator are responsible for obtaining IRB approval of protocol exceptions that may affect the scientific design/integrity of the study, affect the rights, safety or welfare of study subjects, or change the risk/benefit ratio, **prior to implementation**, except where necessary to eliminate apparent immediate hazard to human subject(s). Additionally, when the research involves an investigational device and the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA pre-approval is required [21 CFR 812.150 (4)]. Exceptions necessary to eliminate apparent immediate hazard to human subjects should be reported promptly after initiation.

All Sponsor-Granted Exceptions should be reported using the Request for Modification Form available on the Children's IRB website. **Exceptions must be submitted to the IRB accompanied by documentation of the Sponsor's approval thereof.**

The Principal Investigator must sign the Request for Modification Form prior to submission to Children's IRB.

The Principal Investigator is responsible for obtaining prior Sponsor and IRB approval for protocol exceptions as detailed above, however data collection and communication of such events may be delegated to appropriate clinical site research personnel.

All Sponsor-Granted Exceptions submitted to the IRB will be reviewed. Those deemed appropriate for approval via expedited review will be processed for such approval. All other Sponsor-Granted Exceptions will receive full Board review.

VI. Other Reportable Events and Safety Information:

The following events/information should be reported to Children's IRB within **10 business days**.

- Complaints from research subjects (minor subject complaints that are adequately resolved by the research staff do not need to be reported)
- Adverse sponsor or regulatory agency audit or enforcement action
- Reports, publications, or interim results or findings
    - DSMC (Internal) or DSMB (External) reports and recommendations

    - Regulatory Agency Public Health Advisory
- New or updated study product information
    - Revised Investigator Brochure
    - Revised label / Package Insert
    - Revised Device Manual

Sponsor or regulatory agency recall / withdrawal / clinical hold

Chapter 8 – INFORMED CONSENT

I. The Process of Consent and Assent:

Informed consent for a research study is a process, not just a form and a signature. It includes the recruitment materials, verbal instructions, written materials, question/answer sessions, and the informed consent agreement documented by the subject's signature. Information must be presented in a manner that provides the subject sufficient opportunity to consider whether to volunteer. Furthermore, in the course of communication with a prospective subject or their legally authorized representative, use of exculpatory language (anything through which the subject or the subject's legally authorized representative is made to or appears to waive any of their legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence) should be avoided. The informed consent discussion should occur in an atmosphere that minimizes possible coercion or undue influence. The fundamental purpose of IRB review and approval of the consent document is to protect the rights and welfare of human subjects.

Minors and individuals who are not competent to provide consent should be given the opportunity to assent (affirmational agreement) to participate in the research study. Children's IRB usually requires that individuals who are unable to provide legally effective informed consent on their own, assent to participation whenever possible, and also sign and date a written informed consent / assent document. For research involving minors, Children's policy is that a separate documented assent must be obtained from all children ages 11-17; verbal assent must be obtained from minors ages 5-10 using the same language and required information present in the Children's Assent Form Template. The assent should be written at an age appropriate level.

Informed consent must be presented in a language understandable to the subject (approximately at a 6^{th} to 8^{th} grade reading level), with all required elements of consent included. In addition, no consent document may include exculpatory language. The informed consent document is the written summary of the information provided to the subject and documents the fact that the process of consent occurred. The consent document should be revised if protocol changes warrant it or new safety information becomes available that affects the risks to the participants. All informed consent revisions must be approved by Children's IRB. *Children's Policy 1.61 – Assent and Legally Authorized Representatives Permission in Pediatric Research*

II. Elements of Informed Consent:

The basic elements of informed consent are found in 45 CFR 46.116 and/or 21 CFR 50.25. Federal regulations require that all consent forms contain the following information:

- Introduction (with a statement that the study involves research)
- Purpose of the study
- Description of the study procedures (identifying any that are experimental)
- Expected duration of the subject's participation
- Potential risks or discomforts of participation

- Description of any benefits to the subject or others that may reasonably be expected from the study
- Alternatives that may be available to the subject
- Confidentiality of records description
- Compensation for injury statement (for greater than minimal risk studies)
- Contact persons for answers to pertinent questions about the study, the rights of the subject, and whom to contact in the event of a research related emergency
- Statement that participation is voluntary (no loss of benefits to which the subject is otherwise entitled)
- Statement of who may review their records during the course of the study: Sponsor, Regulatory agencies (DHHS, FDA), Research staff, IRB and all others that may apply
- Dated signature lines to permit verification that consent was obtained prior to participation in the study
- Number of subjects

It is important to include additional elements of information if they are applicable to the study. These include:

- Unforeseen risks statement
- Reasons for involuntary termination of participation (if applicable)
- Additional costs to participants (if applicable)
- Consequences for withdrawal (e.g., adverse health/welfare effects if any)
- New findings statement (to be provided if relevant)
- Compensation

III. Waiver of Informed Consent:

Children's IRB may approve a consent procedure which alters some or all of the required elements or may waive the requirement to obtain informed consent. Requests for a waiver of informed consent must be accompanied by appropriate justification. In general, Children's IRB expects that informed consent will be obtained from all subjects. However, under certain circumstances, an IRB can waive certain requirements for informed consent if the following criteria are met:

1. *Waiver of Documentation of Informed Consent: the regulations (45 CFR 46.117(c)) state that the IRB may waive the requirement for the investigator to obtain a signed consent form if it finds either:

a. the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. The research is not FDA-regulated; or

b. the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

2. *Waiver of Elements of Consent: The IRB may consider waiving the requirement for some or all of the elements of informed consent. The regulations state that informed consent may be waived in full or in part if the IRB determines that:

a. The research involves no more than minimal risk to the subjects;
b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
c. The research could not practically be carried out without the waiver or alteration;
d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation; and
e. The research is not FDA-regulated.

OR:

a. The research or demonstration project is to be conducted by, or subject to the approval of, state or local governmental officials and is designed to study, evaluate or otherwise examine;
    i. Public benefit or service programs;
    ii. Procedures for obtaining benefits or services under those programs;
    iii. Possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs; and
b. The research could not practicably be carried out without the waiver or alteration.

Please complete a *Waiver of Authorization* form (if PHI will be used) along with the explanation for the request within the protocol, which is located on our website.

***Please note, with a few narrow exceptions, FDA regulations do not allow for the waiver of informed consent. The following exceptions are noted in Title 21, as follows**:

a. Documentation of informed consent may be waived if the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. (See 21 CFR 56.109(c))
b. 21 CFR 50.23 and 21 CFR 50.24 outline other conditions where an exception from informed consent requirements may be granted.

IV. Informed Consent and State Law:

State and federal law can differ in a number of ways that may impact the conduct of human subjects research. *Children's Policy 1.80 – Applicability of State Law in Research*

Both FDA and DHHS define a *Legally Authorized Representative* as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in research procedures. Dependant upon applicable law, a Legally Authorized Representative could be a spouse, adult child, sibling, or someone who has been granted durable power of attorney. Children's IRB adheres to the International Conference on Harmonisation's Guideline for Good Clinical Practice, and favors use of the term *Legally Authorized Representative*, defined by the ICH as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Both FDA and DHHS define *children* as persons who have not attained the legal age for consent (under the applicable law of the jurisdiction in which the clinical investigation will be conducted) to treatments or procedures involved in the research or clinical investigations.

Who may act as a Legally Authorized Representative and what, if any, treatments or procedures a "child" can consent to without parental permission vary by local jurisdiction.

It is the responsibility of the Principal Investigator to provide to the IRB any special laws governing medical research, including HIPAA, in the state or community where the clinical investigation will be conducted.

Children's will follow applicable Georgia state law with regards to definitions of child, legally authorized representative, legal representative, adult and emancipated minor.

V. Safeguarding Confidentiality & Protecting Privacy:

Confidentiality and loss of privacy are issues of primary importance in research.

"**Confidentiality**" pertains to the use and disclosure of information (i.e. a subject's Protected Health Information (PHI)). The Principal Investigator must have plans to protect the subjects' identity as well as the confidentiality of the research records. Such plans can include any or all of the following measures: (1) ensuring that all persons who will have access to subjects' PHI have been educated on the HIPAA Privacy Rule; (2) ensuring that all persons who will have access to subjects' PHI have been trained on their respective site's policies relating to confidentiality; (3) requiring that all persons who will have access to subjects' PHI sign a confidentiality agreement or similar obligation to protect the confidentiality of subjects' PHI; (4) limiting access to subjects' PHI to only those persons who need to have access for study-related purposes; (5) using electronic safeguards (i.e. secure data network, limited access to electronic data, password

protections) for PHI that is maintained electronically; (6) using physical safeguards (i.e. storage in a secure, locked area) for PHI that is maintained on paper; (7) removing names and other identifying information from research records; and (8) redacting the identities of study participants when research results are presented at meetings or in medical publications. Other methods of safeguarding confidentiality may also be used.

"**Privacy**" addresses the way(s) a subject is kept from the presence or observation of others and/or protected from unauthorized intrusion(s). The Principal Investigator must have plans to protect the subjects' privacy. Such plans can include any or all of the following measures: (1) limiting personal information collected from subjects to only that which is necessary for study purposes; (2) collecting subjects' personal information in a private setting/location; (3) conducting study-related activities and procedures in a private setting/location; (4) using drapes or other physical barriers for subjects who must disrobe; and (5) leaving study-related phone messages for subjects only in voice mailboxes to which the subject has sole access. Other methods of protecting privacy may also be used.

VI. Subject Compensation:

Compensation for participation in research should not be offered to the subject as a means of coercive persuasion but as a form of recognition for the investment of the subject's time and any other inconvenience incurred. In most cases, compensation should be prorated during the study, to avoid any impression that the investigator is coercing the subject to continue in the study or penalizing the subject for noncompliance with the protocol. Large lump sums at the end of the study are discouraged. These can be seen as an undue influence to the subject continuing in the study, even though they may wish to discontinue.

The Board gives special consideration to vulnerable populations where others are acting as their legally acceptable representatives, that decisions to participate are not based on monetary gain. *Children's Policy 1.78 – Payment of Subjects*

VII. Recruitment:

Advertising and recruiting for study subjects is considered to be the start of the informed consent process. The information contained in the advertisement/recruitment materials and the mode of communication must be reviewed by the IRB and approved before they are used. Any subsequent modifications to approved recruitment materials must also be reviewed and approved by the IRB before use. The materials must be consistent with the IRB approved protocol and informed consent form for the research study and must comply with applicable state and local laws. (See Chapter 5 content regarding Advertisements and Recruitment Materials)

Children's IRB does not want to discourage participation of any who may benefit from research. However, the Board wants to be assured that if special considerations and additional measures need to be taken, they will be implemented. (See Chapter 9 – Vulnerable Subjects, Additional Considerations and Protections) *Children's Policy 1.77 – Recruitment of Subjects*

VIII. Non-English Speaking Subjects:

The informed consent document and all subject materials need to be translated into a language that the subject can read and understand. The translation process is discussed in Chapter 5. The person obtaining the informed consent must be assisted by a translator who is fluent in both English and the language of the subject. *Children's Policy 1.64 – Oral Interpretation for Limited English Speaking (LES) Persons and Written Translation of Consent Forms for Research; also see Chapter 5, Section V of this manual regarding Short Forms.*

IX. Subject Contact with Children's IRB:

It is the responsibility of the Principal Investigator to explain the role of the IRB to prospective subjects. The name and telephone number of the Children's IRB are listed in each informed consent document; a subject may contact the IRB with any questions they may have regarding their rights as a research participant or with any complaints, concerns, or offers of input they may have about the study. *Children's Policy 1.79 – Communication with the Institutional Review Board*

X. Informed Consent Requirements When Determining Eligibility for Research:

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. While an investigator may 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 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. *FDA Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors 1998 Update regarding Screening Tests Prior to Enrollment.*

XI. Signature Requirements:

Research Participant Signature: The study participant must sign and date the consent form. A copy of the consent document will be given to the person signing this document. In emergency, life-saving situations, consent may be waived, but the request must meet the requirements found under 21 CFR 56.109 (c).

Signature of Person Who Conducted the Informed Consent Discussion: The person who conducted the consent discussion must sign and date the consent form.

Investigator Signature: Children's IRB does not require the signature of the investigator on a consent form, but will include this signature block at the request of the Sponsor or Investigator.

Witness Signature: Children's IRB does not require the signature of a witness on a consent form, but will include this signature block at the request of the Sponsor or Investigator. Children's IRB requests that the Sponsor or Investigator have written procedures explaining who may be a witness, and what the witness signature signifies. If

a witness signature block is included on the consent form, it must be signed for each consent form, unless the written procedures of the Sponsor or Investigator allow otherwise.

Impartial Witness Signature: If a research subject or legally authorized representative is unable to read the consent form because of blindness or illiteracy, an impartial witness should be present during the entire consent process, and should sign and date the consent form. Children's IRB may include a signature block for an impartial witness if the sponsor or investigator indicates that the subject population includes subjects who cannot read. The impartial witness signature block should be left unsigned unless there is an impartial witness present for the consent process. The Children's Board may request an impartial witness signature for certain studies. An impartial witness signature block should also be included if required by federal, state or local law.

Signature of Legally Authorized Representatives (LARs): A legally authorized representative is defined as an individual, or juridical or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in a clinical trial. For research studies that allow the enrollment of subjects who are not legally competent, the consent form will include a signature block for an LAR. If the subject is not legally competent, an LAR must participate in the consent process, agree to the subject's participation in the research, and sign the consent form. The IRB must approve the use of an LAR. If the research allows the enrollment of both subjects who are and are not legally competent, then the LAR signature block will be labeled when necessary. This signature block should only be signed if the subject is not legally competent.

Telephone Consent: Verbal telephone consent is not sufficient unless the IRB has granted a waiver of documentation of consent. However, it is acceptable to send the informed consent document by fax and conduct the consent discussion over the telephone when the subject or LAR can read the consent as it is discussed and can provide to the investigator sufficient documentation verifying his/her identity. If the consent is signed, it can be sent back to the investigative site by fax. The consent with original signatures will be mailed or brought to the investigative site at the earliest opportunity and a copy will be given to the subject or LAR.

Chapter 9 – VULNERABLE SUBJECTS, ADDITIONAL CONSIDERATIONS AND PROTECTIONS

For all vulnerable populations, please provide the IRB a detailed explanation of the additional measures taken by your site to ensure the safety and welfare of these potential research subjects. For example, subjects may be given additional time to consider participation, how capacity for consent will be determined, whether the consent of legally authorized representatives is to be sought, whether assent should also be sought, whether an advocate or consent witness should be required and if there will be appropriate follow-up if needed.

I. Children and Minors:

Federal regulations identify four categories of research that may be allowable for children as outlined in 45 CFR 46, Subpart D and 21 CFR 50, Subpart D. The first three categories may be approved by the IRB but the fourth also requires special federal approval.
The Categories are:

1) Research not involving greater than minimal risk. (45 CFR 46.404; 21 CFR 50.51)
2) Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR 46.405; 21 CFR 50.52)
3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR 46.406; 21 CFR 50.53)
4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR 46.407; 21 CFR 50.54)

When children are involved in research, the regulations require the assent of the child (who is capable) and the permission of the parent(s) or legally authorized representative (LAR). Children should always be asked if they want to participate in the research and must affirmatively agree to participate. Children's requires oral assent for children 5 – 10 years of age and a separate documented assent for children 11 – 17 years of age. In certain studies, the IRB may waive assent requirements.

II. Pregnant Women and Fetuses:

Federal regulations at 45 CFR 46, Subpart B require that IRBs consider additional safeguards before approving research involving pregnant women, fetuses, or neonates. Children's typically does not enroll pregnant women, fetuses, or neonates in research studies due to the characteristics of our patient population.

III. Prisoners:

Prisoners, due to the lack of control of their circumstances, are considered to be at greater risk of being coerced into participating in a research study. Special care should be taken that:

- The compensation is not coercive
- The risks of participating would be acceptable to non-prisoner volunteers
- The selection of subjects is equitable and does not affect decisions regarding parole
- Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data are taken
- Adequate follow-up care will be provided, if needed

Only four categories of research are permissible under 45 CFR 46, Subpart C.

The IRB should be notified immediately if an enrolled subject should become incarcerated while participating in a research study. The protocol and consent document would need to be reviewed again with a prisoner representative present. Unless the IRB reapproves the research for the inclusion of the prisoner(s), the newly incarcerated individual must withdraw from the study. Children's typically does not enroll prisoners in research studies due to the characteristics of our patient population.

IV. Cognitively Impaired Persons:

Cognitively Impaired: Having a psychiatric disorder (*e.g.*, psychosis, neurosis, personality or behavior disorders), an organic impairment (*e.g.*, dementia) or a developmental disorder (*e.g.*, mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

In general, Children's IRB will consider the inclusion of cognitively impaired persons only where they are the only appropriate subject population, the research question focuses on an issue unique to subjects in the population, and the research involves no more than minimal risk. Research involving greater than minimal risk may be acceptable where the research is therapeutic with respect to individual subjects (i.e. there is a benefit), and where the risk is commensurate with the degree of expected benefit. Note: Children's IRB usually requires that cognitively impaired persons who are unable to provide legally effective informed consent on their own, assent (provide affirmative agreement) to participation whenever possible, and also sign and personally date a written informed consent / assent document.

The Principal Investigator is in the ideal position to determine if a subject has the ability to understand the implications of the decision to participate in research, and whether the subject is making a rational decision to participate and has the ability to follow the protocol. Since capacity to consent or the ability to withdraw may fluctuate, the investigator should have a process in place for the continued verification of a subject's

understanding and willingness to continue participation throughout the study. If a subject regains the capacity to consent during the study, the investigator should obtain consent from the subject for continued participation. If a person could lose the capacity to consent during the course of the study, the investigator should have a plan to assess continued consent that includes an assessment of capacity, and that provides the subject with the opportunity to appoint a proxy and to provide guidance to the proxy regarding the types of research in which they would not like to participate now or in the future.

V. Traumatized and Comatose:

The manner in which research involving emergency care is conducted shall receive IRB consideration because the subjects' ability to provide informed consent is often severely compromised, and decisions about participation must be made in an expeditious manner and the patient's legally authorized representative may not be available. Altered mental status may arise from trauma, shock, infection, psychological response (anxiety, grief, pain) or the effects of drugs.

OHRP regulations permit waiver of informed consent requirements only in the case of research that presents no more than minimal risk (see 45 CFR 46.116), though the regulation are not "intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state and local laws." FDA regulations permit exception from informed consent requirement for patients confronted with a life-threatening condition where there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the patient's life (see 21 CFR 50.23).

VI. Terminally Ill:

Terminally Ill: Those who are deteriorating from a life threatening disease or condition for which no effective standard treatment exists.

Research involving terminally ill patients presents additional concerns in that potential subjects tend to be more vulnerable to coercion or undue influence than healthy subjects due to their desire to seek treatment, and the research is likely to involve more than minimal risk. Special attention should be given to the informed consent process ensuring the risks and benefits are communicated clearly and in a manner that will neither create false hope nor eliminate all hope.

VII. Educationally Disadvantaged:

Children's IRB shall determine that adequate consideration has been given to the manner in which research involving the recruitment of subjects who are educationally disadvantaged are to be afforded additional protections against coercion and undue influence. This population is considered vulnerable because subjects might be less capable of understanding the nature and risks of the research and may be more subject to coercion.

Illiterate persons who understand English may have the consent read to them and make their mark if appropriate under state law. This may require a witness signature (check with local policy and / or state laws).

VIII. Economically Disadvantaged:

For economically disadvantaged subjects, special consideration should be given to ensure that compensation (whether monetary or other enticements) is not presented in a manner which may be coercive or present undue influence. "Free care" and reimbursements can substantially affect the voluntariness of the decision to participate. Payment should not be contingent on completion of the study and should be prorated.

IX. Wards of the State:

The governmental agency that has control of the Child provides written documentation evidencing its legal authority to give permission for the Child's participation in the study and authorizing a named agency representative to sign appropriate Permission forms on behalf of the child.

If the research protocol either (a) involves greater than minimal risk with no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subjects' disorder or condition; or (b) is research that must be approved under 45 CFR Section 46.406 or .407, or 21 CFR Section 50.53 or .54, then in order for Wards of the State to be considered for enrollment, the IRB must:

- Determine that the research protocol is related to the subjects' status as Wards of the State; or
- it must be conducted in schools, camps, hospitals, institutions or similar setting in which the majority of Children involved as subjects are not Wards of the State;
- Appoint an advocate for each Child who is a Ward of the State, and the advocate shall meet the following qualifications and have the following responsibilities: The advocate will serve in addition to any other individual acting on behalf of the Child as Legal Guardian or in loco parentis. A single person may serve as advocate for more than one Child; the advocate must be an individual who has the background and experience to act in the best interest of the child for the

X. Additional Considerations – Inclusion of Women and Minorities:

Children's IRB shall determine whether consideration has been given to the manner in which subjects are selected and assure that adequate provision has been made for the inclusion of women and minorities, whenever possible. The benefits and burdens of research should be distributed fairly within society and investigators should always seek racial and gender equity in the recruitment of subjects.

X. Additional Protections – Students, Employees and Normal Volunteers:

Students: Students who participate in research in their own student setting (university, medical school).

There can be many potential problems with student participation in research. It is important to ensure that consent is freely given and not coerced. Students may feel the need to agree to participate in research in order to receive favor with the faculty, academic credit, monetary compensation, better grades, employment, recommendations, or other reasons. Another concern with student research is confidentiality, due to the close nature of a college environment.

Guidelines should be established to ensure that confidentiality and coercion do not become areas of concern in the academic research setting.

Normal Volunteer: A healthy person who volunteers for medical research and for whom no therapeutic benefit can result from participation.

The altruistic motivation for the normal volunteer's agreement to participate in research heightens the concern for the risks to which such participants should ethically be exposed. Monetary payments should not be so great that they constitute an undue inducement. Any compensation that is offered should be commensurate with the time, discomfort, and risk involved.

Employees: Employees of the hospital/university/research center.

It is important to ensure that employees who volunteer to participate in research where they are employed are not coerced in any manner. Their decision to participate, or not to participate, should have no impact on their performance evaluations, job advancement, or employment status. Guidelines should be established to handle an injury or illness of an employee who is participating in research. Due to the close nature of a research environment, strict measures should be taken to ensure the confidentiality of an employee's study-related records.

Chapter 10 – RESEARCH CONFLICTS AND NONCOMPLIANCE

I. Conflict of Interest:

Situations arise in which financial or other personal situations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting and reporting research. The evaluation for assessing a potential bias to the mandate of human subject protections is very important. Children's IRB has a financial disclosure section as a part of its Submission Application for Investigator and Study Staff. If any information provided in the financial disclosure section changes during the course of the study, or within one year after the last participant completed the study as specified in the protocol, Children's IRB must be immediately notified. *Children's Policy 1.58 – Conflict of Interest Related to Research*

The Principal Investigator has the responsibility to assess conflict of interest for each study and all study staff, and re-assess throughout the study. If conflict of interest becomes an issue, a report must be made to the IRB.

OHRP has published guidance for protecting research subjects from possible harm caused by financial conflicts of interest in research studies. The guidance document is entitled Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection.

The guidance is located at: http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf

II. Noncompliance and Complaint Reporting:

The Principal Investigator bears the ultimate responsibility for the conduct of the research study.

The Principal Investigator must comply with the IRB's policies and requirements as well as all regulatory requirements on the federal, state and local level.

Information regarding noncompliance in research may come to the attention of the IRB in many different ways. Reports of noncompliance may arise from new submission applications, continuing review reports, internal audits, safety reports, complaints from subjects in research, concerns from research sites, reports of protocol noncompliance (including information from monitoring letters or sponsor correspondence), failure or repeated failures of the Principal Investigator to file requested reports to the IRB, whistleblower information, publications written by Principal Investigators without IRB approval of the referenced study(ies), and regulatory agency audit reports regarding an investigator or a study.

Investigators and research staff are required to report any observed, suspected or apparent noncompliance to the IRB. This refers to all noncompliance, not just serious or continuing noncompliance. *Children's Policy 10.14 – Reporting Noncompliant Conduct in Research and Policy 1.79 – Communication with the Institutional Review Board*

III. Suspension or Termination of IRB Approval:

The appropriate regulatory agency and Sponsor (if applicable) will be notified of any determination made by the Board to suspend or terminate approval of a research study or investigative site. The Principal Investigator will be sent a letter detailing the IRB's determination, and the length of suspension or termination of IRB approval. Any response from the Principal Investigator, Sponsor/CRO or regulatory agencies will be reviewed by the IRB. *Children's Policy 1.16 – Institutional Review Board Standard Operating Procedures*

IV. Appeal of IRB Decisions:

The investigator may appeal the decision of the IRB to disapprove a protocol after the final review with the investigator in attendance at the convened IRB meeting. The investigator will submit the appeal to the Director of Clinical Research. The Director of Clinical Research 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 Director of Clinical Research.

Approval by the IRB of research protocols may be subject to further appropriate review by the Director of Clinical Research. 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.

Neither the Principal Investigator, Institution nor Sponsor has the authority to overrule the IRB's disapproval or suspension/termination of a study or activity. *Children's Policy 1.16 – Institutional Review Board Standard Operating Procedures*

Chapter 11 – SPECIAL TOPICS

I. HIPAA:

HIPAA stands for the Health Insurance Portability and Accountability Act of 1996. The Privacy Rule establishes the conditions under which certain healthcare groups, healthcare clearinghouses, organizations, or businesses, called "covered entities," handle the individually identifiable health information known as Protected Health Information (PHI). Principal Investigators should be aware of the Privacy Rule because it establishes the conditions under which covered entities can use or disclose PHI for research purposes. The specific regulations for HIPAA are found in: 45 CFR 160 and 164.

Many research organizations that handle PHI will not have to comply with the Privacy Rule because they are not covered entities. The Privacy Rule will not directly regulate researchers who are engaged in research within organizations that are not covered entities even though they may gather, generate, access, and share personal health information. For instance, entities that sponsor health research or create and/or maintain health information databases may not themselves be covered entities; however, the Privacy Rule may affect their relationships with covered entities. It is recommended that research sites consult their own legal counsel to determine if they are a "covered entity". See the decision tool entitled "Covered Entity Charts" available at:

http://www.cms.hhs.gov/HIPAAGenInfo/Downloads/CoveredEntitycharts.pdf

Covered entities are permitted to use or disclose protected health information for research with individual authorization, or without individual authorization under limited circumstances as set forth in the Privacy Rule.

*****NOTE: Children's Healthcare of Atlanta is a covered entity*****

Authorization by Research Participant/Parent/Guardian/Legally Authorized Representative:

HIPAA specifies that a covered entity may neither use nor disclose PHI for research purposes unless the patient has provided, in advance, his or her written authorization for such use or disclosure (unless a waiver is obtained). It is the responsibility of the PI to be aware of any state and local laws that raise the standard that HIPAA has set forth.

Six Required Elements:

- A description of the PHI to be used or disclosed that specifically identifies the information
- Name of the persons and/or entities authorized to use or disclose the PHI
- Name of the persons and/or entities authorized to receive the PHI
- The purpose of the requested use or disclosure of PHI
- An expiration date, which may be indicated as "end of study" or "none," for Authorization to place PHI in a research database
- Signature of the subject and date

Three Required Statements:

- A statement that the subject has the right to give written notice to withdraw their authorization at any time, including any applicable exceptions to the right to withdraw authorization
- A statement that once the subject's PHI has been disclosed, it is possible that the receiver may re-disclose the information
- A statement that informs the subject that they may choose to refuse to sign the authorization and this will not affect their medical treatment

General Requirements:

- The authorization must be written in plain language (approximately 8th grade level and translated as needed)
- A copy of the authorization form must be given to the subject

Waiver or Partial Waiver of Authorization:
For research uses and disclosures of PHI, Children's IRB may approve a waiver or partial waiver of authorization. Partial waivers are likely to be sought to enable investigators to contact and recruit individuals as potential research subjects. The following criteria must be satisfied to grant a waiver or partial waiver of authorization:

- The use or disclosure of protected health information involves no more than minimal risk to the individuals based on at least the presence of:
    - An adequate plan to protect PHI identifiers from improper use and disclosure
    - An adequate plan to destroy PHI identifiers at the earliest opportunity consistent with the research (unless there is a health or research justification, or it is required by law)
    - Adequate written assurances against re-disclosure of the PHI (except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by regulation)
- Practicability: The research could not practicably be conducted without the Partial Waiver/ Waiver
- Access: The research could not practicably be conducted without access to and use of the PHI

II. Emergency Use of Investigational Drug or Device:

Definitions:
Emergency Use means the use of a test article (e.g., investigational drug, biologic, or device) 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 (21 CFR 56.102(d)). For the purposes of 21 CFR 56.102(d), "life-threatening" includes the scope of both life-threatening diseases/conditions and severely debilitating diseases/conditions.

Life-threatening means 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. 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 means diseases 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.

FDA and the IRB recognize that situations arise in which there could be a need to use an investigational drug, biologic, or device in a manner inconsistent with the approved protocol or by a physician who is not an investigator on the clinical study. The criteria for emergency use are defined in the Code of Federal Regulations (CFR) and must be followed. The emergency use provision in 21 CFR 56.104(c) is an exemption from prior IRB review and approval and may not be used unless all provisions of 21 CFR 56.102(d) exist. This exemption allows one use without prospective IRB review, and FDA requires that the IRB is notified within 5 working days of the emergency use of the test article. Any subsequent use requires prospective IRB review and approval.

OHRP regulations do not provide for an emergency use exception to IRB review, though OHRP regulations do allow physicians to provide emergency medical treatment to patients. In emergency use situations, OHRP regulations do not consider patients to be research subjects.

For *approval* of a test article's use in an emergency situation, a full Board review is required (expedited or subcommittee review/approval is not allowed). However, if the conditions of 21 CFR 56.102(d) are met but it is not possible to convene a quorum within the time available, the IRB Chairman or appropriate designee (a Board member with appropriate medical knowledge) may *acknowledge* notification of the emergency use.

The investigator seeking acknowledgement of emergency use of a test article should provide the IRB with a letter documenting the presence of each of the following conditions:

a. a life-threatening situation exists in which no standard acceptable treatment is available
b. the test article must be used expeditiously, meaning insufficient time is available to convene a quorum for full-Board IRB review/approval

This notification to the IRB must occur within 5 working days of use of the test article.

The IRB Chairman or appropriate designee will review the investigator's letter of notification, and will only *acknowledge* emergency use of a test article if each of the following conditions exist to justify the use:

a. a life-threatening situation exists in which no standard acceptable treatment is available
b. the test article must be used expeditiously, meaning insufficient time is available to convene a quorum for full-Board IRB review/approval

If the IRB Chairman (or designee) confirms the presence of the necessary conditions, the IRB Chairman (or designee) will sign/send a letter to the investigator acknowledging notification of emergency use of the test article. If the Sponsor requires a written acknowledgement from the IRB in order to approve shipment of the test article, Children's IRB will provide the Sponsor a copy of its acknowledgement letter to the investigator.

FDA Guidance for IDE Early/Expanded Access:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm

FDA IRB Information Sheets – Drugs and Biologics –
http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html

There are many considerations regarding patient protections in emergency use. Please contact Children's IRB if you are contemplating emergency use of a test article.
Children's Policy 1.60 – Emergency Use of Investigational Drugs, Biological Products and Devices

III. Humanitarian Use Device:
A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 people in the United States per year. To be considered for HUD status, a device sponsor must submit a humanitarian device exemption (HDE) application to the FDA. The applicant must demonstrate that no comparable devices are available for the use intended for the device in question and that the applicant device could not be brought to market without the conditions of the HDE.

Role of the IRB: This is the only situation where federal regulations require the IRB to approve and monitor an activity that is not considered research. The application must be submitted prior to review and approval by the Board. The IRB is responsible for initial and continuing review of all HUDs.

IV. Expanded Use of Investigational Drugs
Expanded access is the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options.

FDA regulations allow access to investigational drugs for treatment purposes on a case-by-case basis for an individual patient, or for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial. They also permit expanded access for large groups of patients who do not have other

treatment options available, once more is known about the safety and potential effectiveness of a drug from ongoing or completed clinical trials.

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. **Individual patients, including for emergency use**
   The FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician. The criteria in 21 CFR 312.305 and 312.310 must be met.

2. **Intermediate-size patient populations**
   The FDA may permit an investigational drug to be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol. The criteria in 21 CFR 312.05 and 312.315 must be met

3. **Treatment IND or treatment protocol**
   The FDA may permit an investigational drug to be used for widespread treatment use. The criteria in 21 CFR 312.05 and 312.20 must be met.

For specific guidance, see 21 CFR 312, Subpart I, or contact the IRB.

V. Genetic Research:

Genetic research typically presents risks of social and psychological harm to participants rather than risks of physical harm. The Board will consider the following areas when reviewing a genetic testing protocol or sub-study:

- Selection of participants
- Confidentiality and privacy
- Disclosure of information
- Secure storage of data and biological samples
- Participant withdrawal (possible continued risk with long term storage of biological samples)
- Assessment of predictive value of the research study

VI. Investigator Held IND/IDE:

When an investigator holds an IND/IDE, they must fulfill both the Principal Investigator and Sponsor responsibilities. Please contact Children's IRB for assistance.