Protocol TEMPLATE: Intervention Study (Clinical Trials)

This template can be modified to accommodate a variety of intervention study designs. Sections that are not applicable can be deleted. Delete the sections in blue or red and save the final document with all “track changes” accepted before submission.

Additional information for using this template with examples for each section is available on the [IRB website](https://irb.research.chop.edu/protocol-templates). The investigator is strongly advised to review this information before writing his/her protocol.

|  |  |  |
| --- | --- | --- |
| Title: | **Complete Title** | |
| Short Title | eIRB will request a short title of up to 5 words for tracking purposes | |
| Drug or Device Name(s): | XXXXX | |
| FDA IND | (if applicable) XXX-XX | |
| Regulatory Sponsor: |  | |
| eIRB Number |  | |
| Protocol Date: |  | |
| Amendment 1 Date: | | Amendment 3 Date: |
| Amendment 2 Date: | | Amendment 4 Date: |
| **Sponsor** (IND or IDE holder, if applicable) Sponsor Name Address City, State, Zip Country | | |
| **Study Principal Investigator** (if multicenter study with CHOP PI responsible) Office Address City, ST, ZIP Phone XXX-XXX-XXXX email: XXXXX@XXX.XXX | | |
| **Site Principal Investigator** The Children’s Hospital of Philadelphia Office Address Philadelphia, PA, 19104 Phone XXX-XXX-XXXX email: XXXXX@chop.edu | | |

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Be sure to update the Index after the protocol is finalized. In MS Word, update using the INSERT menu, Index and Tables.

# Abbreviations and Definitions of Terms

|  |  |  |
| --- | --- | --- |
|  |  | Insert and delete terms as relevant |
| °C |  | Degrees centigrade |
| AE |  | Adverse event |
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# Abstract

Use JAMA format (http://jama.ama-assn.org/misc/ifora.dtl#Abstracts). Limit to 150 – 200 word abstract, written for lay members. This abstract is used in the IRB database and in the minutes of meetings.

Context: (Background)

Include 1 - 3 sentences about the clinical importance of the condition and the importance of the research question.

Objectives: (primary and important secondary objectives)

State the precise objective or study question

If more than 1 objective, limit to only the key secondary objectives.

Study Design:

Basic design: Randomized controlled trial, cohort study, case-control study, cross-sectional study, etc.

Setting/Participants:

The setting including location (referral or community center) and level of care (inpatient or outpatient)

The number of sites

The number and description of participants including key eligibility criteria

Study Interventions and Measures:

Study drug, or other intervention and main monitoring procedures

Main study outcome measures (assessments of primary and key secondary endpoints)

# Protocol Synopsis

(Do NOT include a Synopsis if submitting protocol for expedited review)

|  |  |
| --- | --- |
| **Study Title** | LIMIT SYNOPSIS to no more than 2 - 3 pages. The synopsis should provide a rapid overview of the study for lay members and for members who are not the primary reviewers. Keep the synopsis BRIEF. Use bullet points. |
| **Funder** | Grant Agency, Pharmaceutical company, or Departmental funds |
| **Clinical Phase** | (Phase I, II, III or IV - if applicable) |
| **Study Rationale** | No more than ½ page |
| **Study Objective(s)** | **Primary**   * To determine (obtain, evaluate, verify, etc.) …   **Secondary**   * To determine (obtain, evaluate, verify, etc.) … |
| **Test Article(s)**  *(If Applicable)* | Describe the study drug, device, diagnostic, diet or other intervention |
| **Study Design** | Overview of design. Explain the basic design such as parallel group randomized controlled trial, open-label single arm PK study, diagnostic test evaluation, etc. |
| **Subject Population**  **key criteria for Inclusion and Exclusion:** | **Inclusion Criteria**   1. Subjects age X – X 2. Include main criteria but does not need to be complete, etc.   **Exclusion Criteria**   1. Subjects with X or Y, etc. |
| **Number Of Subjects** | Total Number of Subjects, Total Number at CHOP, Total Number of Sites |
| **Study Duration** | Each subject’s participation will last … |
| **Study Phases**  **Screening**  **Study Treatment**  **Follow-Up** | The study phases listed at the left are **examples only**. Intervention studies have at least 2 phases: (1) Screening: screening for eligibility and obtaining consent and (2) Intervention: study intervention/experimental treatment. |
| **Efficacy Evaluations** | Primary evaluation measurements that will be used to assess the efficacy of the intervention |
| **Pharmacokinetic Evaluations** | *(include only if applicable)* |
| **Safety Evaluations** | Primary measurements that will be used to assess safety |
| **Statistical And Analytic Plan** | Limit to discussion of analysis to primary endpoint and possibly main secondary endpoint |
| **Data And Safety Monitoring Plan** | Describe how is responsible for data quality management and ongoing assessment of safety: PI, independent medical monitor, internal safety committee, or DSMB |

# EXAMPLE: Table 1: Schedule of Study Procedures

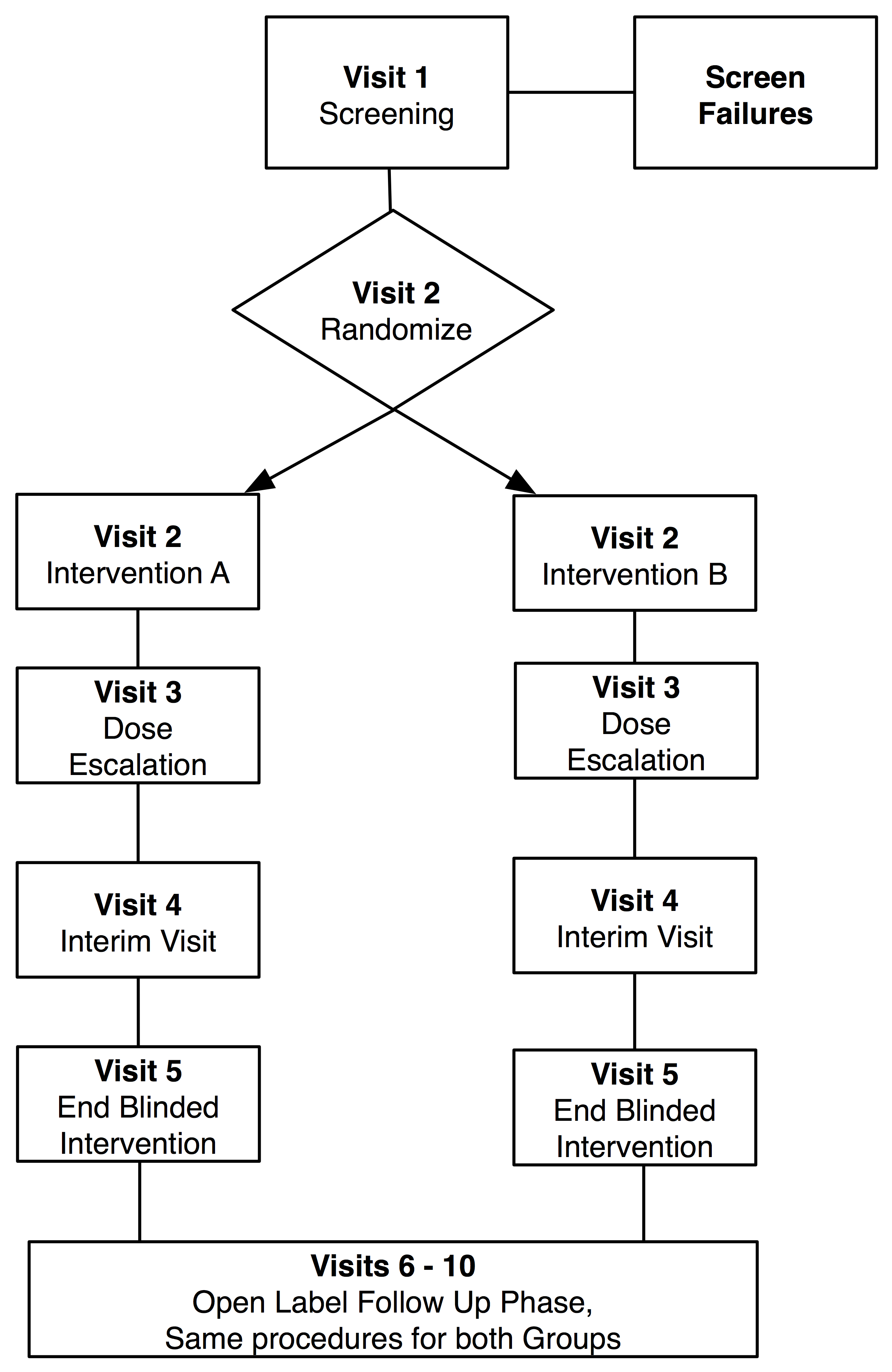
|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Phase** | **Screening** | **Treatment/Intervention** | | | **Open-Label Treatment** | | **Follow-up** | | |
| **Visit Number** |  | **1** | **2** | **3** | **4** | **5** | **6** | **7 a** | **8** |
| **Study Days** |  |  |  |  |  |  |  |  |  |
| Informed Consent/Assent | X |  |  |  |  |  |  |  |  |
| Review Inclusion/Exclusion Criteria | X |  |  |  |  |  |  |  |  |
| Demographics/Medical History | X |  |  |  |  |  |  |  |  |
| Physical Examination | X |  |  |  |  |  |  |  |  |
| Vital Signs: BP, HR, RR | X |  |  |  |  |  |  |  |  |
| Height and Weight | X |  |  |  |  |  |  |  |  |
| Pregnancy Test | X |  |  |  |  |  |  |  |  |
| Prior/Concomitant Medications | X |  |  |  |  |  |  |  |  |
| Clinical Laboratory Evaluation | X |  |  |  |  |  |  |  |  |
| Randomization |  |  |  |  |  |  |  |  |  |
| Dispense Study Drug |  |  |  |  |  |  |  |  |  |
| Drug Compliance |  |  |  |  |  |  |  |  |  |
| Adverse Event Assessment |  |  |  |  |  |  |  |  |  |

This table is an example of a schedule of procedures. The Investigator should construct a table based on the procedures in the protocol. If the study involves more than 1 or 2 visits, it is often preferable to include this table as an Appendix to the Consent Form. This simplifies the consent form.

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# EXAMPLE: Figure 1: Study Diagram

A flow diagram of the study may be relevant to explain the flow of subjects in the trial. An example flow diagram for randomized, controlled clinical trial design is included as an example below.



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# Background Information and Rationale

Section 1 should be no more than 3 – 5 pages. Refer the reader to the applicable grant, or attached literature references for more detailed information.

## Introduction

Brief paragraph or two to describe the setting and rationale for the study. The details of the background go into Section 1.6

## Name and Description of Investigational Product or Intervention

Name and description of the study intervention (drug, device, diagnostic, diet, experimental psychological therapy, etc.). If a drug, device or biologic, the specific description, packaging, control systems will go in Section 7.

## Findings from Non-Clinical and Clinical Studies

(This section is only applicable for drugs, biologics and devices)

### Non-Clinical Studies

### Clinical Studies

#### Human Pharmacokinetics

#### Clinical Studies in Adults

#### Clinical Studies in Children

## Selection of Drugs and Dosages

Description of dosage forms available and those to be used in study

## Relevant Literature and Data

Overview of the literature and data relevant to the trial and provide background for the trial. Also the relevant literature establishing the validity for scales, evaluation tools etc. The reference citations should be listed at the end in Section 11. It is usual to limit this to 10 (at most 20) key references.

## Compliance Statement

This study will be conducted in full accordance all applicable Children’s Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). Note: Only include the sections of Title 21 if the study is regulated by the FDA. Only include ICH compliance if the study will actually comply with these requirements. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children’s Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

# Study Objectives

State the overall objectives of the study.

The purpose of the study is to determine the (efficacy, pharmacokinetics, safety etc.) of ….

## Primary Objective (or Aim)

The primary objective of this study is to determine the whether the XXX (intervention) reduces, increases, etc. outcome measure XXX in children X to X years. This should be specific, for example: “to determine if enalapril decreases systolic blood pressure after 4 weeks compared to placebo.”

The primary objective should be both the most important and the objective on which the study sample size is based. Objectives (aims) are usually phrased in some variant of “…to determine…”. Protocols differ from grants in that they do not usually enumerate specific hypotheses. If included, these belong in the Analysis section.

## Secondary Objectives (or Aim)

The secondary objectives are to:

* Determine if there is a relationship between X to Y.
* Determine the pharmacokinetics of drug X.
* Evaluate the tolerability and safety of XXXX for short-term administration in the stated population.

# Investigational plan

## General Schema of Study Design

Section 3 is a brief overview of the study design. In Sections 3.1.1 – 3.1.4 include brief overview of the study phases (Screening, Baseline assessment, Treatment Phase, Follow-Up, etc.).

Section 3.1 is intended to be a brief overview. Do not put the details of the entire study into this Section. Section 4 is where the details of the study and its procedures belong. A description of the study design should be included, e.g., randomized controlled trial, concurrent or non-concurrent (retrospective) cohort study, case-control study, cross sectional study, pharmocokinetic-pharmacodynamic study, descriptive study, natural history study, evaluation of a diagnostic, etc. Provide a general description here and a general description of the various phases in Sections 3.1.1, 3.1.2, etc.

Reference to Figure of Study Schema and to Table of Procedures as applicable.

### Screening Phase

How will subjects be identified and screened. NOTE: Informed consent, subject assent, and HIPAA authorization (as applicable) should be discussed in Section 9.6.1.

For example, *“Potential subjects will be screened using the protocol inclusion and exclusion criteria. Subjects will be recruited into two strata: children 6-12 years of age, and children 13-16 years of age with a goal of 50% of subjects per age strata.*

*Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study related procedures being performed, including discontinuation of current therapy. Blood samples will be drawn to confirm eligibility based on clinical laboratory parameters. Females ≥ 11 years of age will have a urine pregnancy test.”*

### Study Treatment Phase (start of the study intervention)

Description of Phase 1 of the study (or the entire main study, if there is only one phase).

### Phase 2 (Use an appropriate descriptor such as “Open-label Treatment”)

(*If applicable*) Description of Phase 2 of the study.

### Follow-up Phase

(*If applicable*) To be eligible for the follow-up phase, subjects must either have (1) ……

The follow-up phase will continue for up to XXXX days.

## Allocation to Treatment Groups and Blinding

Briefly describe the method for treatment allocation and blinding (if applicable). If the study is randomized provide an overview of the process. Details about who will generate the randomization sequence, how the sequence will be generated (table of random numbers, computer, etc.), stratification, blocking, etc. should be included in Section 9.1.

## Study Duration, Enrollment and Number of Sites

### Duration of Subject Study Participation

This section refers to the duration of the subject’s participation, not the duration of the study from the investigators’ standpoint. The study duration per subject will be up to XXX days, with up to XXX days screening, up to XXX days Phase 1, up to XXX days Phase 2, and XXX days follow-up.

### Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at approximately XX investigative sites in the United States and XXXX. (NOTE: CHOP and all of its satellite locations are considered one site).

Recruitment will stop when approximately XXX subjects are ….. It is expected that approximately XXX subjects will be enrolled to produce XXXX evaluable subjects. (NOTE: Enrolled subjects are those who consent to participate. Evaluable subjects are enrolled subjects whose data is used in the final analysis. The evaluable goal cannot be larger than the enrolled goal.)

## Study Population

*The study population for every type of study design is defined by Inclusion and Exclusion criteria. A few examples are included below.*

Define the study population using inclusion and exclusion criteria, regardless of study design. For each subject group, there needs to be separate inclusion/exclusion criteria. For example, the control population may have different selection criteria than the population with the disease or condition of interest.

### Inclusion Criteria (examples)

### Index/Case Subject Inclusion Criteria

1. Males or females age X to XX years
2. Diagnosis of XX
3. Weight ≥ XX kg
4. Girls ≥ 11 years of age must have a negative urine/serum pregnancy test.
5. Parental/guardian permission (informed consent) and if appropriate, child assent.
6. Additional criteria as required

### Index/Case Subject Exclusion Criteria

1. Laboratory abnormalities that indicate clinically significant hematologic, hepatobiliary, or renal disease (EXAMPLE below):

AST/SGOT > 2.0 times the upper limit of normal

ALT/SGPT > 2.0 times the upper limit of normal

Total bilirubin > 2.0 times the upper limit of normal

Hemoglobin < 9 gm/dL

White blood cell count < 3,000/ mm3

Platelet count < 100,000/mm3

1. Pregnant or lactating females
2. Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures
3. Additional exclusion criteria as applicable

### Control Subject Inclusion Criteria

1. Males or females age X to XX years
2. Additional inclusion criteria as applicable

### Control Subject Exclusion Criteria

1. Exclusion criterion 1
2. Additional exclusion criteria as applicable

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# Study Procedures

This section should list the procedures, observations, measures, etc. at each study visit, including history, examination, study drug administration or other interventions. Section 4 lists what will be done. Section 5 describes how it will be done. For complicated studies with several visits, it is recommended that the investigator create a Table of Procedures (page x).

## Screening Visit (delete if screening is solely performed by reviewing the medical chart)

List the timing and all of the procedures to be performed at the screening visit. This can be a simple bullet list.

* Informed Consent/Assent/HIPAA authorization (See the IRB’s webpage on [Recruitment vs Screening](https://irb.research.chop.edu/recruitment-vs-screening) for more information on whether consent is required for screening)
* Physical Exam
* Vital Signs
* Laboratory tests
* Medical Record Review

## Study Treatment Phase

General overview of this phase.

### Visit 1

Detailed description of study visit including all procedures. This is usually included as a simple bullet list of all of the interventions, monitoring procedures and measurements that will take place. The study coordinator should be able to quickly review the list of procedures at each visit in order to correctly execute the study.

* Physical Exam
* Vital Signs
* Laboratory tests
* Start study intervention
* Dispense study diary
* Medical Record Review

### Visit 2

Detailed description of study visit including all procedures.

* Physical Exam
* Vital Signs
* Laboratory tests
* Collect unused study drug
* Dispense study drug
* Assess possible adverse events
* Medical Record Review

### Visit 3

* Physical Exam
* Vital Signs
* Laboratory tests
* Collect unused study drug
* Dispense study drug
* Assess possible adverse events
* Medical Record Review

## Phase 2 of the Study (e.g. Open-Label Treatment)

(Only include if applicable) General description of the phase.

### Visit 4

Detailed description of study visit including all procedures – listed like above examples.

### Visit 5

Detailed description of study visit – listed like above examples.

## Follow-up Phase (only if applicable)

General overview of this phase.

### Visit 6

Detailed description of study visit including all procedures – listed like above examples.

### Visit 6: End of Study

Detailed description of study visit including all procedures – listed like above examples.

## Unscheduled Visits

Description of how unscheduled visits will be handled.

## Concomitant Medication

(Include if appropriate) Example: *All prior and concomitant medications used within XX days prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.*

## Rescue Medication Administration

*If subjects may receive rescue medication for adverse reactions or inadequate response to study medication, the options and how the decision will be made to permit such treatment should be included here.*

## Subject Completion/Withdrawal

Criteria for withdrawal of subjects and plans for provision of care after withdrawal. Example: *Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to REASON (list). The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.*

### Early Termination Study Visit

List the procedures that will be performed for each subject that withdraws prior to completing the study. Example: *Subjects who withdraw from the study will have all procedures enumerated for Visit XXX as the early termination visit.*

# Study Evaluations and Measurements

Every monitoring procedure, measurement and intervention listed in Section 4 should have a corresponding description of exactly how the measurement will be made. Each evaluation, BP, QOL questionnaire, etc. should be listed with a description here. A copy of any non-standard measurement tool should be attached as an appendix. The IRB website contains a list of validated measurement tools that do not need to be appended to the protocol or application.

Examples of evaluations are included below. Inclusion of data collection forms or case report forms is not required but every data element that is collected should be described along with how it will be measured. Standard, validated tests and test instruments do not have to be included in the Appendix but non-standard and non-validated instruments should be included.

## Screening and Monitoring Evaluations and Measurements

### Medical Record Review

Include a listing of the variables that will be abstracted from the medical chart (paper or electronic).

* Date of birth
* Weight
* Etc.

### Physical Examination

Describe the baseline evaluations including the medical history, physical examination, demographic characteristics (age, gender, race) and other information that will be collected.

### Vital Signs

Describe which measures will be made and how they will be made. Example: will BP be measured with an automated device or with an aneroid sphygmomanometer? Which arm will be used? Sitting or lying down? Will more than one BP measurement be made and averaged?

### Laboratory Evaluations (only list those performed for research purposes, not those performed as part of clinical care)

#### Table: Clinical Laboratory Tests (validated tests performed in a CLIA/CAP lab)

|  |  |
| --- | --- |
| **Category** | **Tests** |
| Hematology | RBC, hemoglobin, hematocrit, platelet count, WBC with differential |
| Liver function tests | SGOT/AST, SGPT/ALT, total Bilirubin |
| Renal function tests | BUN, creatinine |

#### Research Laboratory Tests (non-validated tests performed in a research lab)

* Exploratory Biomarkers

#### Pregnancy Testing

(If appropriate) A urine pregnancy test will be performed for female subjects ≥ 11 years of age and girls <11 years who are physically capable of becoming pregnant.

### Other Evaluations, Measures

Describe other rating scales, tests, psychological tools, laboratory evaluations, etc.

## Efficacy Evaluations

These are the measures that will be used to assess the efficacy of the study intervention. The discussion of these evaluations is usually more detailed.

### Diagnostic Tests, Scales, Measures, etc.

Methods and timing the measures that will be used to assess efficacy

## Pharmacokinetic Evaluation

(only if applicable) Sampling for pharmacokinetics will be …. The parameters determined will be … Both model independent and model-dependent methods will be used. etc.

## Safety Evaluation

Example: Subject safety will be monitored by adverse events, vital signs, physical examinations, laboratory data (QQQQ rating scales (AAA, BBB, and CCC). It will also include YYYY and ZZZZ examinations/evaluations/scales, etc.

# STATISTICAL CONSIDERATIONS

This section should provide sufficient detail to permit assurance that the sample size is justified and the statistical methods sufficient and appropriate for the research question(s).

## Primary Endpoint

The primary endpoint is the variable that relates back to the Primary Objective and serves as the basis for the justification for the Sample Size.

Example: The primary endpoint will be the change in Variable1 between Screening and Visit X*.*

## Secondary Endpoints

Secondary endpoints will include the following:

* The change in ……
* The change in …..
* Safety and tolerability of DRUG based on Adverse Events. Measurements and evaluations

## Statistical Methods

### Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects randomized at Visit 1.

The primary efficacy endpoint will be the change in XXX between Visit X and Visit Y.

Secondary endpoints will include the change in XXX.

### Pharmacokinetic Analysis

Description of pharmacokinetic parameters to be assessed and methods to be employed to calculate those parameters:

### Safety Analysis

Example: All subjects entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

## Sample Size and Power

Sample size justification and power analysis *(if appropriate)*. All studies must include a justification for the chosen sample size even if a power analysis isn’t appropriate (for example a PK study). The basis for how the size was chosen should be explained. Any assumptions made (mean and SD), clinically important differences, and the details of the calculation should all be included.

## Interim Analysis

Interim efficacy or safety analyses if planned and include a description of stopping rules for efficacy and stopping rules for safety. Stopping rules for efficacy should generally be limited to life-threatening and serious diseases.

# Study Medication (Study DEVICE or OTher Study INTERVENTION)

## Description

A description of the study drug, device or other intervention should be included here. Omit sections that do not apply.

### Packaging

Clinical supply description

### Labeling

Description of product label

### Dosing

XXX can be taken as a \…. Directions for use

### Treatment Compliance and Adherence

Assessment of compliance and requirements for continuation in the trial

### Drug Accountability

Who will maintain the receipt and disposition records for study medications? For example: Adequate records of study drug receipt and disposition will be maintained by the CHOP Pharmacy Records of receipts, investigational drug orders, dispensing records, and disposition forms will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities and the Sponsor that the investigational new drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol. At study completion, all drug supplies including partially used and empty containers must be returned to Sponsor or designee.

# SAFETY MANAGEMENT

This section provides two generic safety management plans. One is for greater than minimal risk studies; the second is for minimal risk studies (in red). This section should be consistent with CHOP IRB Guidelines tailored to the requirements for each study. For example, it may be appropriate to exclude scheduled hospitalizations from inclusion as an SAE or if the study is observational and does not involve an intervention, to propose limiting SAE reporting to those AEs directly related to the study and not to underlying illness.

## Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

## Adverse Event Reporting

The Investigator is responsible for recording and reporting unanticipated problems related to research that occur during and after study treatment. The plan for Adverse Event reporting should be consistent with the CHOP IRB Guidelines. Two examples are included below, one for greater than minimal risk and one for minimal risks studies.

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

**For Minimal Risk Studies use the following paragraph instead of the one above.**

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that do not meet prompt reporting requirements will be summarized in narrative or other format and submitted to the IRB at the time of continuing review (if continuing reviews are required), or will be tracked and documented internally by the study team but not submitted to the IRB (if continuing reviews are not required).

For minimal risk studies the remainder of the Section 8 may be deleted.

## Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

## Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

* death,
* a life-threatening event (at risk of death at the time of the event),
* requires inpatient hospitalization or prolongation of existing hospitalization,
* a persistent or significant disability/incapacity, or
* a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

### Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

## IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report. (External events that don’t change the risks to subjects or result in a change to the research protocol or consent form usually do not require reporting to the IRB. See the IRB website for SAE reporting requirements.)

|  |  |  |
| --- | --- | --- |
| **Type of Unanticipated Problem** | **Initial Notification  (Phone, Email, Fax)** | **Written Report** |
| Internal (on-site) SAEs Death or Life Threatening | 24 hours | Within 2 calendar days |
| Internal (on-site) SAEs All other SAEs | 7 days | Within 7 business days |
| Unanticipated Problems Related to Research | 7 days | Within 7 business days |
| All other AEs | N/A | Brief Summary of important AEs may be reported at time of continuing review |

### Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator’s assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

## Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting must be consistent with regulatory, sponsor or GCRC requirements (if applicable)

## Medical Emergencies

(If applicable) Describe any plans or procedures for taking care of medical emergencies that might develop during the course of the study.

# STUDY ADMINISTRATION

## Treatment Assignment Methods

### Randomization

Procedures for generation, maintenance and execution of the randomization schedule.

### Blinding

Describe the procedure for maintaining the study blind (if any) for subjects, investigators and trial personnel.

### Unblinding

Procedures, if any, for unblinding of study personnel during the conduct of the study.

## Data Collection and Management

Describe the system for maintaining primary records (source documents), case report forms, screening data (both for subjects who are eligible and enrolled in the main study and for individuals who are screening failures, when applicable), and for entering the data into any computerized systems. The plan should be consistent with [CHOP Policy A-3-6](https://at.chop.edu/communities/policyprocedure/administrative/Active/a-3-9.pdf): Acceptable Use of Technology Resources that defines the requirements for encryption and security of computer systems. Address the following:

1. Confidentiality. How will the confidentiality of the data be ensured, from abstraction though analysis?

* One method is to keep a master list containing PHI and subject ID number separate from data forms (paper and electronic) that have only a study ID number. The master list should be on a separate computer, removable disk drive or in a locked file cabinet. This form of data is considered “coded” not de-identified. As long as the data can be re-linked to identifiers, the data is coded. Only when the key to the code or the Master List is destroyed are the data considered de-identified.
* Another method is to use password-protected files; in Excel, type “password” in the Help box for instructions. NOTE: if any of the investigators who access identifiable data are not in the CHOP workforce, there are important HIPAA rules on disclosure. The investigators and IRB may also need to consider whether the external investigator(s) is engaged in the research.
* Data files can be encrypted

1. Security. Have a plan for backing up or otherwise recovering data. This can be as simple as a copy of the password-protected file on your office computer, with the original in one of the Hospital’s secure servers.
2. Anonymization, de-identification or destruction. Provide a specific plan for removing identifiers that meets the needs of the study and potential future uses of the data. Be sure that data retention procedures meet the requirements of the study sponsor and CHOP Data Retention Policy A-3-9.

## Confidentiality

Include a statement that all data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Describe the safeguards to maintain subject confidentiality.

No identifiable data will be used for future study without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

## Regulatory and Ethical Considerations

### Data and Safety Monitoring Plan

Describe the data safety and monitoring plan (DSMP). Include the processes and safeguards that will be in place to identify risks to research subjects and to protect subjects during the execution of the trial. See IRB SOP 803 for additional details. The plan should be tailored to the risks of the study intervention and the nature of the disease process and should provide oversight for the emerging safety information could include one or more of the following:

* Principal Investigator
* Medical Monitor associated with the sponsor or the study
* Independent Safety Officer,
* Internal Steering Committee or Internal Data Monitoring Committee made up of representatives of the sponsor and study investigators;
* Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) made up of representatives who are independent of the study sponsor and investigators.

Certain studies (late Phase 2 and Phase 3 trials, particularly for life-threatening diseases) may be required to include an independent Data and Safety Monitoring Board (DSMB) that will be in place to monitor the safety events associated with the study. If a DSMB will be employed, the full details of the composition of the DSMB, how it will operate, and how the interim analyses are to be performed should be provided.

The CHOP PI will monitor and review the study progress, subject safety, and the accuracy and security of the emerging data.

### Risk Assessment

Risks are either not greater than minimal, a minor increase above minimal or greater than minimal. Describe the risks of each research intervention or procedure in terms of magnitude and probability of harm. Consider all physical, psychological, economic, or societal harms that might accrue to subjects or others.

Distinguish between risks associated with routine clinical care from those that will occur as a result of research. Summarize the overall anticipated risks from the study intervention and study-related procedures.

Address how the study design and execution will minimize the risks of harm.

### Potential Benefits of Trial Participation

Summarize all potential benefits, if any from trial participation. Benefits should be broken down into direct benefits (accrue to the study subject as a result of participation) and indirect benefits (benefits that accrue to the individual or society in the future).

### Risk-Benefit Assessment

The Risk-Benefit assessment should include justification for proceeding with the trial based on the balance between risks and benefits.

## Recruitment Strategy

Describe the approach to recruiting subjects. Where will they come from? How will the investigator identify prospective subjects? Will the subjects come from the investigator’s patients or will they be patients of other care providers? If the prospective subjects are not patients of the investigator who will first approach the subjects and by what method (in person, via mail, via telephone contact?) Will advertising be used (note: all recruitment materials that subjects will see and/or hear must be reviewed and approved by the IRB before they are used to recruit subjects)? Will there be sufficient subjects to achieve the study goals?

If eligibility screening requires collection of data about prospective subjects (via medical record review, direct query or other procedures), and this screening will take place before subjects consent to participation in the main study, describe the plan for obtaining consent/assent and HIPAA authorization for the screening (unless the screening either qualifies for waivers of consent/assent/HIPAA authorization or does not require prior informed consent/assent/HIPAA authorization [see Section 9.6.1 for additional information]).

For more information, see the IRB’s webpage on the differences between [Recruitment vs Screening](https://irb.research.chop.edu/recruitment-vs-screening).

## Informed Consent/Assent and HIPAA Authorization

Describe the procedures that will be used to obtain informed consent/HIPAA Authorization and assent. Include: who will obtain consent and assent, where will consent/assent process take place, how privacy will be assured (e.g. the consent conference will occur in a private exam room), how much time will subjects be permitted to make a decision, how the investigators will assure that subjects comprehend the nature of the study, the study procedures and the risks and benefits of participation, steps that will be taken to avoid coercion and documentation of consent. Also, include whether a stand-alone HIPAA Authorization will be used or a combined consent-authorization document.

If the study includes several populations or scenarios for obtaining consent, create subsections to address them (e.g. for those who provide consent/assent/HIPAA authorization in person, those who provide consent/assent/HIPAA authorization over the phone, etc.).

### Screening

Describe the process for screening procedures, including location (e.g. in person, over the phone, etc.) and consent/assent/HIPAA authorization determinations request (e.g. written or verbal consent/assent/HIPAA authorization will be obtained, written or verbal consent/assent will be obtained, written or verbal HIPAA authorization will be obtained, waivers of consent/assent/HIPAA authorization are requested, etc.). If no screening procedures will be conducted, delete this sub-section.

The IRB may approve screening procedures without obtaining the prior informed consent of the prospective subject or the subject’s legally authorized representative only if the solicited information is **limited to the minimum necessary for screening/determining eligibility** for the main study AND if these procedures are limited to: (a) obtaining information through oral or written communication with the prospective subject or legally authorized representative, or (b) obtaining identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens. **NOTE:** If the information or biospecimens used for the purpose of screening, recruiting, or determining the eligibility of subjects include protected health information (PHI), HIPAA applies and HIPAA Authorization may still need to be obtained prior to conducting these screening activities. See the IRB’s webpage on [Recruitment vs Screening](https://irb.research.chop.edu/recruitment-vs-screening) for more information.

### Main Study

Describe the consent process for main study procedures, including location (e.g. in person, over the phone, etc.) and consent/assent/HIPAA authorization determinations request (e.g. written or verbal consent/assent/HIPAA authorization will be obtained, written or verbal consent/assent will be obtained, written or verbal HIPAA authorization will be obtained, etc.).

### Consent/HIPAA Authorization Plan for Subjects Who Reach Age of Majority

Describe the consent/HIPAA authorization process for individuals who become legal adults while enrolled in the study. If subjects will provide verbal consent/HIPAA authorization for their continued participation (e.g. if they are contacted over the phone), make sure all study materials request a waiver of documentation of consent and alteration of HIPAA (to obtain verbal authorization), and that a verbal consent/HIPAA authorization form is provided. If no subjects will reach the age of majority while enrolled, delete this section.

### Individuals with Limited English Proficiency

Describe the consent/assent/HIPAA authorization process for individuals with limited English proficiency. If subjects will be enrolled over the phone, also outline the role of the interpreter in the phone conversation (i.e. will they be physically present with the investigator or conferenced into the call, how will interpreters/witnesses document their role in the consent process, etc.).

### Waiver of Consent

If the study appears to qualify for waiver of consent (studies limited to existing data), the protocol must provide sufficient information explaining why the research meets the criteria of 45 CFR 46.116(f)(3) so that the IRB can grant the request. The eIRB application will request this same information.

**45 CFR 46.116(f)(3)** An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver or alteration;

(4) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; and

(5) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

### Waiver of Assent

When the subjects of the research are children, a waiver of consent means a waiver of parental permission and assent (the IRB must waive both). The criteria of §116(f)(3) listed above must be met to obtain a waiver of assent.

Assent could also be waived (with or without a waiver of parental permission) under 45 CFR 46.408, if the capability of some or all of the children is so limited that they cannot reasonably be consulted or if the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

In either case, the request to waive assent must be justified and appropriate for the study being proposed.

### Waiver of HIPAA Authorization

The criteria for waiver of HIPAA Authorization are similar to, but different than those for waiver of consent.

**45 CFR 164.512(i)(2)(ii)** A statement that the IRB or privacy board has determined that the alteration or waiver, in whole or in part, of authorization satisfies the following criteria:

(A) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

(1) an adequate plan to protect the identifiers from improper use and disclosure;

(2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

(3) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

(B) The research could not practicably be conducted without the waiver or alteration; and

(C) The research could not practicably be conducted without access to and use of the protected health information.

See the IRB website for more information about [Waivers of Consent, Assent and HIPAA](https://irb.research.chop.edu/waivers).

## Payment to Subjects/Families

If subjects or parents/guardians are to be paid for the inconvenience of participating in the study, the amount of payment(s) must be stated in the protocol. The amount paid to parent/guardians should be separated from the amount paid to subjects. The IRB must review both the amount and method of payment to subjects to ensure that neither presents an undue influence on the trial subjects. Subjects not completing the study, for whatever reason, must be paid on a pro rata basis.

See the [IRB SOP 704](https://irb.research.chop.edu/sites/default/files/documents/irbsop704_payments_9-25-18_group.pdf) and [Payments to Subjects](https://irb.research.chop.edu/payments-subjects) on the IRB website.

### Reimbursement for travel, parking and meals

Amount per visit, justification and form of reimbursement.

### Payments to parent for time and inconvenience (i.e. compensation)

Amount per visit, justification and form of payment.

### Payments to subject for time, effort and inconvenience (i.e. compensation)

Amount per visit, justification and form of payment.

### Gifts

If any tokens of appreciation will be given to subjects or families, these should be described here.

# PUBLICATION

Describe the plans for publication and confirm that only aggregate data without individually identifiable information will be published. If the CHOP investigator will not have access to the complete study data, describe how publication will proceed.

# References

All references belong in this section.

# Appendix

Append relevant information.