Protocol TEMPLATE: Intervention Study (Clinical Trials)

This template can be modified to accommodate a variety of intervention study designs.

1. Please note all instructions are in BLUE and all examples are in BLACK.
2. Sections that are not applicable to this protocol may be deleted.
3. You may add other sections if you feel they are necessary.
4. For any section that is addressed in both the SmartForm and attached protocol, the content must be consistent.

Investigators are advised to review this document before drafting a protocol to ensure familiarity with the details that are required.

|  |  |
| --- | --- |
| Title: | **Complete Title** |
| Drug or Device Name(s): | XXXXX |
| FDA IND/IDE | (if applicable) XXX-XX |
| Regulatory Sponsor: |  |
|  |  |
| Protocol Date: |  |
| Amendment 1 - Date: |  |
| Amendment 2 - Date: |  |
| Amendment 3 – Date: |  |
| Amendment 4 – Date: |  |
|  |  |
| Principal Investigator: |  |
| BCH IRB Protocol Number: |  |

Abbreviations and Definitions of Terms

Define any abbreviations or terms.

Example:

|  |  |
| --- | --- |
| °C | Degrees Centigrade |
| AE | Adverse Event |
|  |  |
|  |  |
|  |  |

Protocol Synopsis

The synopsis should provide an overview of the study that is accessible to individuals without a medical background.

* Keep the synopsis BRIEF.
* Use bullet points.
* Use lay language as much as possible and avoid overly technical terms.

|  |  |
| --- | --- |
| Study Title | Title |
| Funder | Grant agency, pharmaceutical company, or departmental funds |
| Clinical Phase  *(If applicable)* | Phase I, II, III, or IV |
| Study Rationale | No more than ½ page |
| Study Objective | 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. |
| Participant Population | **Inclusion criteria**   1. Participants age X – XX 2. Include main criteria, but does not need to be complete, etc.   **Exclusion Criteria**   1. Participants with X or Y, etc. |
| Number of Participants | Total Number of Participants   * Total number at BCH * Total number at all sites if a multicenter study |
| Study Duration  *(if specified)* |  |
| Duration of each participant’s participation  *(could be a range)* |  |
| Study Phases | Example of phases:   * Screening * Study Treatment * Follow-up   Intervention studies usually have at least 2 phases:   1. Screening: Screening for eligibility and obtaining consent and 2. Intervention: Study intervention/experimental treatment |
| Primary Endpoint | Primary endpoint and measurements that will be used to assess them |
| Secondary Endpoints | Secondary endpoint and measurements that will be used to assess them |
| Safety Evaluations | Primary measurements that will be used to assess safety |
| Statistical and Analytical Plan | Limit to discussion of analysis to primary endpoint and possibly main secondary endpoint |
| Data and Safety Monitoring Plan (DSMP) | Describe who is responsible for data quality management and ongoing assessment of safety: PI, independent medical monitor, internal safety committee, or Data Safety Monitoring Board (DSMB) |

Example – Table 1: Schedule of Study Procedures

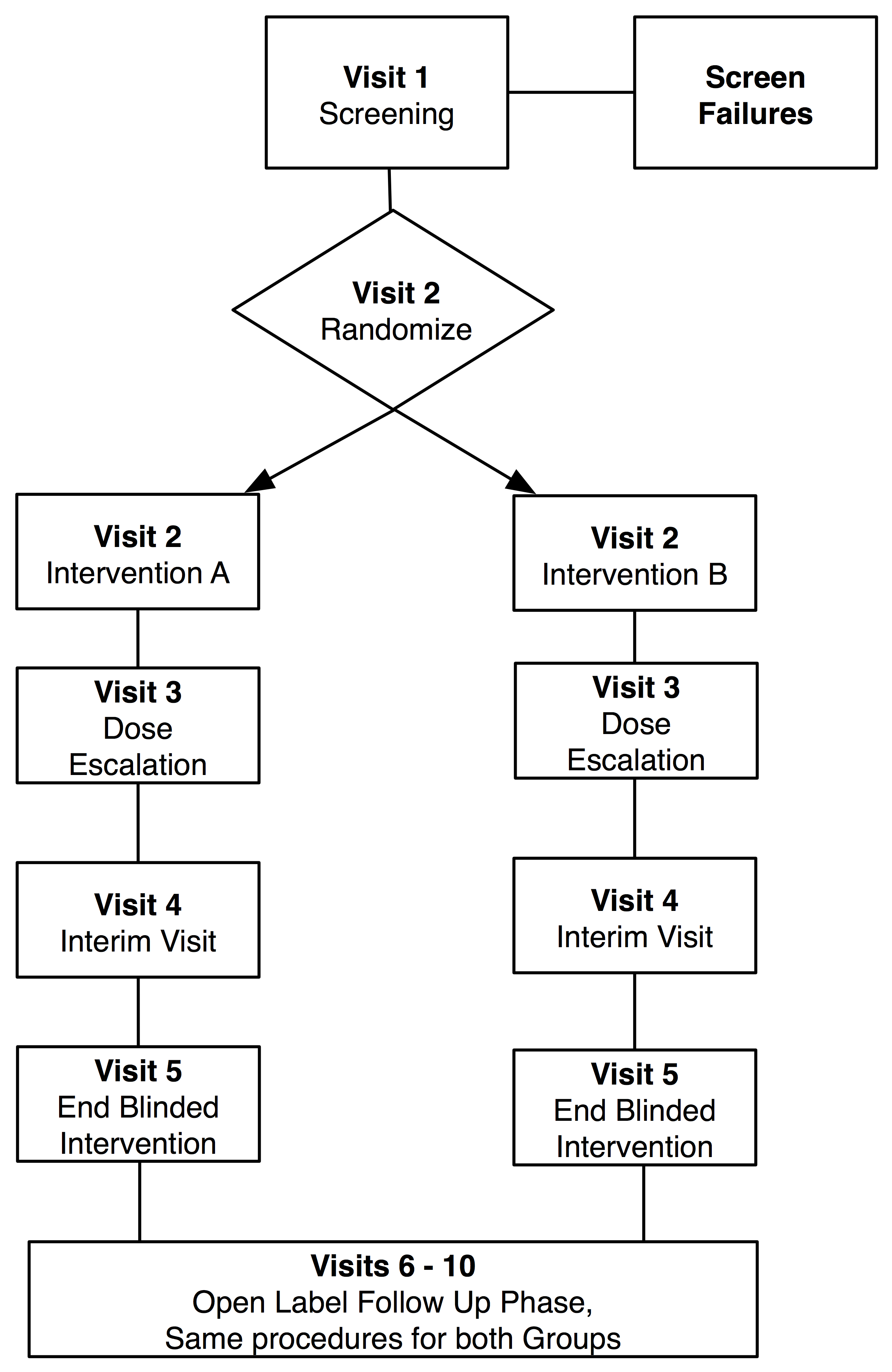
This table is an example of a schedule of procedures. The Investigator should construct a table based on the procedures in the protocol. If the study involves more than 1or 2 visits, a table should be include in the Consent Form or as an Appendix to the Consent Form. This may also be moved and included with section 4.

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

# Example – Figure 1: Study Diagram

A flow diagram of the study may be relevant to explain the flow of participants in the trial. Whenever possible do not copy the detailed table from the manual of operations and rather format this as a simplified flow diagram. This may also be moved and included with section 3.

Example: Randomized controlled clinical trial design



**1. Introduction**

**1.1 Study Rationale**

**Describe the setting and rationale for the study**.

* Include background information for the following (this information should be linked to the study rationale as relevant):
* a description of the disease, including the mechanism
* the burden and epidemiology of the disease
* the population(s) and demographics of the populations affected
* If there are subgroups, describe and address any variability in safety/efficacy/etc. by subgroup
* unmet medical needs or specific requirements of the population and/or subgroup
* available drugs and/or intervention(s) for treatment, including treatments by subgroup, if applicable
* Address whether the population that you are enrolling has similar demographics to the disease population for whom the intervention is intended

**1.2 Findings from Non-Clinical and Clinical Studies**

**Include findings from animal studies and studies in adults and/or children,** *as applicable,*

**1.3 Relevant Literature and Data**

**Include an overview of the literature and data relevant to the trial and provide background for the trial, and relevant literature establishing the validity for scales, evaluation tools, etc.**

2. Study Objectives and Design

* A study objective is a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behavior).

Do not include hypotheses in this section. If there are hypotheses, they belong in the Analysis section.

**2.1 Primary Objective (or Aim)**

**State the primary objective of this study.**

This is the most important objective which generally drives the statistical planning (e.g., calculation of sample size to provide appropriate power for statistical planning).

|  |
| --- |
| Examples:   * The primary objective of this study is to determine the whether the X intervention reduces … * The purpose of the study is to determine [efficacy, pharmacokinetics, safety etc.] of … |

**2.2 Secondary Objectives (or Aim)**

**State the secondary objective(s).**

|  |
| --- |
| Examples:   * Determine if there is a relationship between X to Y. * Evaluate the tolerability and safety of XX for short-term administration in the stated population. |

3. Investigational Plan

**3.1 General Schema of Study Design**

Section 3.1 is intended to be a brief overview of the study design. Please note, Section 4 is where the study details and procedures belong.

**Provide a general description of the study design**, which should include (as applicable):

* Indicate if single-site or multi-site
* Type of trial: e.g., randomized controlled trial, concurrent or non-concurrent (retrospective) cohort study, case-control study, cross sectional study, pharmacokinetic-pharmacodynamic study, descriptive study, natural history study, evaluation of a diagnostic, etc.
* Description of each study phase (e.g., screening, study treatment, follow-up, etc.)

**3.2 Study Duration, Enrollment, and Number of Sites**

*3.2.a* **Duration of Study Participation for each Participant**

**Describe the duration of participant’s participation, not the duration of study.**

|  |
| --- |
| Example:  The study duration per participant will be up to #days, with up to #days for screening, up to #days for Phase 1, up to #days for Phase 2, and #days for follow-up. |

*3.2.b* **Total Number of Study Sites/Total Number of Participants Projected to Enroll**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**Specify the total number of**:

* Study Sites
* Planned Enrolled participants (those who consent to participate)
* Projected Evaluable participants (enrolled participants whose data is used in final analysis). This number may be lower than the number of enrolled participants if it is expected that some participants will withdraw.

*\* Please note that the evaluable goal cannot be larger than the enrolled goal*

|  |
| --- |
| Examples:   * The study will be conducted at approximately X sites in the United States and will enroll XX participants. * It is expected that X participants will need to be enrolled to produce XX evaluable participants. |

**3.3 Study Population and Recruitment**

For each participant 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.

*3.3.a* **Inclusion/Exclusion Criteria for each participant group**

Consider the following:

* Exclusion must be scientifically, medically, and ethically justified.
* If there are subpopulation, inclusion criteria may need adjusted for laboratory and other differences by subgroup
* As appropriate, accessibility efforts and provisions for populations such as individuals:
* with disabilities
* whose preferred language is other than English (or the preferred language of the region)
* who are transgender or non-binary. Note that in data collection:
  + Sex and gender should be reported as different variables.
  + Consider when and how sex and gender will be collected and reported.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Examples:  **Index/Case Participant Inclusion Criteria**   1. Individuals age X to XX years 2. Diagnosis of XX 3. Individuals able to give birth ≥ 11 years of age must have a negative pregnancy test.   *Consider referencing “Individuals able to give birth” and “their partners,” rather than specifying any sex or gender.*  *“Able to give birth” is defined as the individual is in puberty as defined by Tanner stage or menarche.*   1. Parental/guardian permission (informed consent) and if appropriate, child assent.   **Index/Case Participant Exclusion Criteria**   1. Laboratory abnormalities that indicate clinically significant renal disease  |  |  | | --- | --- | | AST/SGOT | > 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 |  1. Pregnant or lactating individuals 2. Parents/guardians or participants who in the opinion of the Investigator may not be complaint with study schedules or procedures   **Control Participant Inclusion Criteria**   1. Individuals age X to XX years 2. Additional inclusion criteria as applicable   **Control Participant Exclusion Criteria**   1. Exclusion criterion 1. 2. Additional inclusion criteria as applicable |

*3.3.b* **Recruitment Strategy**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

* **Describe the approach to recruiting participants**, including:
* how you are ensuring that the study cohort is representative of the population with the disease/disorder under study.
* efforts of inclusion and accessibility.
* *If considered*, **provide details about how culturally and linguistically appropriate recruitment methods and materials will be used and their development** (e.g., working with a community advisory board, working with Boston Children’s Hospital’s Office of Health Equity, and Inclusion (OHEI), etc.).
* **Detail where and how potential participants will be recruited by providing the following information**:

1. Where will participants come from?
2. How will the investigator identify prospective participants?
3. Will the participants come from the investigator’s patient pool, or will they be patients of other care providers?
   1. If the prospective participants are not patients of the investigator, who will first approach the participants and by what method (e.g. in person, via mail, via telephone contact)?
4. Will advertising be used?
   1. All recruitment materials, visual and auditory that will be presented to potential participants must receive prior review and approval from the IRB before being utilized in participant recruitment.

* **Describe if eligibility screening requires collection of data about prospective participants** (via medical record review, direct query or other procedures), and if this screening will take place before participants consent to participation in the main study.

4. Study Procedures

This section should list the procedures, observations, measures, etc., including history, examination, or other monitoring procedures and measurements. This is usually included as a simple bullet list of all the procedures that will take place at each visit. Items to note:

* 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.

The study should consider efforts that enable ease of participant accessibility. Examples could include, but are not limited to doing virtual visits, night and weekend hours, using local labs, and/or home health care for visits. If possible, include provisions or efforts to accommodate individuals who may have challenges with transportation, employment, or childcare. Visit frequency should be minimized to the extent possible, while still aligning with the objectives of the study.

**4.1 Screening Visit**

**Create a simple list of the timing and all the procedures to be performed at the screening visit. Indicate NA if screening is conducted solely through medical chart review.**

|  |
| --- |
| Example:   * Informed Consent/Assent/HIPAA authorization [See the IRB’s webpage on Recruitment vs Screening for more information on whether consent is required for screening) * Physical Exam * Vital Signs * Abdominal Ultrasound * Brain MRI * DEXA Scan * Electrocardiogram (ECG) * Laboratory Tests * Questionnaires * Medical Record Review |

**4.2 Study Intervention Phase**

**Provide a general overview of this phase**. This can be a simple bullet list of all 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 to correctly execute the study. In this section detailed tables that are often part of larger studies can be included.

|  |
| --- |
| Example:  **Visit 1**   * Physical Exam * Vital Signs * Abdominal Ultrasound * Brain MRI   **Visit 2**   * Physical Exam * Vital Signs * Laboratory Tests * Questionnaires |

**4.3 Phase 2 of the Study (i.e. Open Label Extension, whereby all participants receive active study drug/device/intervention)**

**Provide a general overview of this phase***, if applicable*. This can be a simple bullet list of all the interventions, monitoring procedures and measurements that will take place.

|  |
| --- |
| Example:  **Visit 3**   * Physical Exam * Questionnaires * Laboratory Tests |

**4.4 Follow-up Phase**

**Provide a general overview of this phase***, if applicable*. This can be a simple bullet list of all the interventions, monitoring procedures and measurements that will take place.

|  |
| --- |
| Example:  **Visit 4**   * Physical Exam * Questionnaires * Laboratory Tests |

**4.5 Unscheduled Visits.**

**Describe how unscheduled visits will be handled.**

**4.6 Concomitant Medication**

*If applicable:*

|  |
| --- |
| 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. |

**4.7 Rescue Medication Administration**

**Include a description about the potential provision of rescue medication for adverse reactions or inadequate response to study medication, specifying the options, and how the decision will be made to permit such treatment**, *if applicable.*

**4.8 Participation Completion/Withdrawal**

**Describe the withdrawal process of participants and plans for provision of care after withdrawal.**

* Participants 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, Adverse Events (AEs), or due to [REASON] (i.e., provide list).
* The Investigator or the Sponsor may also withdraw participants who violate the study plan, or to protect the participant for reasons of safety or for administrative reasons. It will be documented whether or not each participant completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the participant completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

Consideration*: Track sociodemographic characteristics of withdrawal and early terminations to* monitor for patterns/impact on certain groups.

**4.9 Early Termination Study Visits**

**List the procedures that will be performed for each participant that withdraws prior to completing the study.**

|  |
| --- |
| Example:  Participants who withdraw from the study will have all procedures enumerated for Visit XXX as the early termination visit. |

5. Study Procedures

**For each monitoring procedure, measurement and intervention listed in Section 4, describe 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 and non-validated instrument should be attached as an appendix. Standard validated tests and test instruments do not have to be included.
* Inclusion of data collection forms or case report forms are not required.

**5.1 Screening and Monitoring Evaluation and Measurements**

*5.1.a* **Medical Record Review**

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

|  |
| --- |
| Example:   * Date of birth * Weight * Additional data points as applicable |

### *5.1.b* Physical Examination

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

*5.1.c* **Vital Signs**

**Describe which measures will be taken and how they will be made.**

Possible descriptions to provide:

* 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?

*5.1.d* **Clinical Laboratory Evaluations for Research Purposes**

**Only list evaluations performed for research, not performed as part of clinical care**.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Example:  ***Clinical Laboratory Tests – Validated tests performed in a CLIA/CAP lab***   |  |  | | --- | --- | | **Category** | **Tests** | | Hematology | RBC, hemoglobin, hematocrit, platelet count, WBC w/differential | | Liver function tests | SGOT/AST, SGPT/ALT, total Bilirubin | | Renal function tests | BUN, creatinine | |

*5.1.e* **Research Laboratory Tests – Non-validated tests performed in a research lab**

**Only list evaluations performed for research, not performed as part of clinical care.**

|  |
| --- |
| Example: Exploratory Biomarkers |

*5.1.f* **Pregnancy Testing**

*If applicable*: Remember that pregnancy testing in adolescents and decisionally impaired adults requires accepting responsibility for communication of positive results to the child in a fashion that respects their privacy.

|  |
| --- |
| Example:  A urine pregnancy test will be performed for all individuals capable of becoming pregnant ≥ 11 years of age and those <11 years who have had a menstrual period. |

### *5.1.g* Other Evaluations, Measures

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

**5.2 Efficacy Evaluations**

**Describe the measures that will be used to assess the efficacy of the study intervention**

*5.2.a* **Diagnostic Tests, Scales, Measures, etc.**

**Describe the methods and timing the measures that will be used to assess efficacy.**

*5.2.b* **Pharmacokinetic Evaluation**

*If applicable:*

|  |
| --- |
| Examples:   * Sampling for pharmacokinetics will be …. * The parameters determined will be … * Both model independent and model-dependent methods will be used, etc. |

**5.3 Safety Evaluation**

|  |
| --- |
| Example:  Participant safety will be monitored by adverse events, vital signs, physical examinations, laboratory data (Q rating scales (A, B, and C). It will also include Y and Z examinations/ evaluations/ scales, etc. |

6. 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). The statistical analysis plan should include whether and how subgroup population differences will be evaluated and reported.

If there are hypotheses, in this section those can be outline with a description of the analyses that address the hypotheses.

**6.1 Primary Endpoint**

**Describe the 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. |

**6.2 Secondary Endpoints**

**List the secondary endpoint(s)**.

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

**6.3 Statistical Methods and Analysis**

*6.3.a* **Baseline Data**

**Describe how 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).

*6.3.b* **Efficacy Analysis**

|  |
| --- |
| Examples:   * The primary analysis will be based on an intention to treat approach and will include all participants 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. |

*6.3.c* **Pharmacokinetic Analysis**

**Describe the pharmacokinetic parameters to be assessed and methods to be employed to calculate those parameters**, *if applicable.*

*6.3.d* **Safety Analysis**

|  |
| --- |
| Examples:   * All participants who 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. |

*6.3.e* **Special considerations**

* **Selection bias, subgroup exclusion, and loss to follow-up**

Examining screen failure rates and data are important to determine if there is selection bias and whether the resulting data is representative. It is important to assess whether certain subgroups are disproportionately impacted by the screening process. This section of the protocol should address how screen failures will be reviewed to identify potential disparity in subgroup exclusion. Investigators may consider scheduled study participant reviews during the study to evaluate if sample stratification is occurring and if recruitment efforts are not reaching certain groups (i.e. marginalized patients historically underrepresented in research or those primarily affected by the diagnosis). These scheduled reviews give the PI time to review recruitment strategies and potentially further recruitment efforts to assure equitable access and inclusion.

The protocol application should provide a plan to review participant loss-to-follow-up, considering both demographic and non-demographic factors. Examining discontinuation/withdrawal rates and associated data are important to identify any patterns that may emerge. Further, it is important to assess whether there is selection bias that could potentially impact the generalizability of the study results.

The statistical analysis plan should include whether and how subgroup population differences will be evaluated and reported.

* **Considerations of Race/ethnicity in the Interpretation of Results and Impact**: Studies that focus on differences by certain subgroups, such as race/ethnicity have the potential to perpetuate theories of biological inferiority and discriminatory behavior. The study team should be mindful of how they interpret the results so as not to draw conclusions that individuals who have been historically underrepresented in research, from marginalized populations, and/or medically underserved populations are more likely to have negative outcomes (i.e., surgical complications) through some fault of their own – rather than considering potential structural factors. While the study team cannot influence how others interpret their work, the study team could help ensure their work is not used to perpetuate biases by carefully considering and focusing on how they describe and discuss their results, the language used in the title, and presentations and manuscripts that present study findings.
* **Guidance**: [AAMC](https://www.ama-assn.org/system/files/ama-aamc-equity-guide.pdf) and [CDC Health Equity Style Guides](https://www.cdc.gov/healthcommunication/Resources.html).

**6.4 Sample Size Power**

**Include sample size justification and power analysis**, *if applicable.*

All studies must include a justification for the chosen sample size even if a power analysis isn’t appropriate (i.e. 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 be included. Make sure there is adequate power to consider subgroups (e.g., race/ethnicity) if that is part of the purpose of the study.

**6.5 Interim Analysis (efficacy or safety)**

**Include a description of stopping rules for efficacy and stopping rules for safety**, *if applicable*. Stopping rules for efficacy should generally be limited to life-threatening and serious diseases.

7. Study Drug/Device or other intervention

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**7.1 Description**

**Include a description of the study drug, device or other intervention should be included here,** *if applicable.*

*7.1.a* **Packaging**

**Include clinical supply description.**

### *7.1.b* Labeling

**Include product label description.**

### *7.1.c* Dosing

|  |
| --- |
| Examples:   * XXX can be taken as a… * Directions for use… |

### *7.1.d* Treatment Compliance and Adherence

**Assessment of compliance and requirements for continuation in the trial**

### *7.1.e* Drug Accountability

**Who will maintain the receipt and disposition records for study medications?**

|  |
| --- |
| Example:  Adequate records of study drug receipt and disposition will be maintained by the BCH 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 participant 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. |

**8. Adverse Events and Serious Adverse Events**

**8.1 Definitions**

*8.1.a* **Definition of an Adverse Event**

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

**Provide the definition of an AE being used for the study.**

*8.1.b* **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 participant.

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 – events may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Provide the definition of a SAE being used for the study.**

*8.1.c* **Definition of Unexpected**

AEs or suspected adverse reactions that are mentioned in the IB, package insert, or device labeling as occurring with a class of drugs (or other medical products) or as anticipated from the pharmacological properties or other characteristics of the study intervention, but are not specifically mentioned as occurring with the particular study intervention under investigation. Expectedness is assessed based on the awareness of AEs previously observed, not on the basis of what might be anticipated from properties of study intervention.

**List role/person who will determine expectedness and provide the source(s) of the reference safety information used to determine expectedness (e.g., IB, approved labeling, etc).**

|  |
| --- |
| Example:  [Insert role] will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. |

**8.2 Identification and Classification of AEs and SAEs**

The Investigator is responsible for recording all AEs and SAEs related to research that occur during and after study treatment. For each AE and SAE, with a full description of the event, including the following:

* 1. Expectedness
  2. Severity of the event
  3. Relationship to study intervention
  4. Duration and Frequency: date and time of onset
  5. Outcome of the event

*8.2.a* **Severity of Event**

**Describe method of grading severity and intensity of event** (e.g., Mild, Moderate, Severe)

*8.2.b* **Relationship to Study Intervention**

**Describe the method of determining the relationship of an AE to a study intervention (e.g., Related vs. Not-related; Definitely, Probably, Potentially, Unlikely or Not Related)**

*8.2.c* **Time Period and Frequency for Event Assessment and Follow-up**

**Describe how AEs and SAEs will be identified and followed until resolved or considered stable. Specify timeframes and procedures for recording and follow-up of AEs and SAEs**

**8.3 Reporting AEs, SAEs and other Unanticipated Events**

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) are required to be reported to the IRB in accordance with BCH IRB policy: Reportable Events: Unanticipated Problems and Adverse Events Involving Risks to Research Subjects and Others

Policy/Procedure.

**Describe the reporting procedures for the IRB, Sponsor and regulatory agencies as applicable, including timeframes.** Further details could be included or described through:

* Manual of Operations
* Standard Operating Procedures (SOPs)
* Description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the reports, and who will receive notification of reports .

**8.4 Medical Emergencies**

**Describe any plans or procedures for taking care of medical emergencies that might develop during the study***, if applicable:*

**8.5 Multi-Site Safety Monitoring**

If this is a multi-site study, describe plans for coordination of safety monitoring. Describe the processes for communication among sites concerning information relevant to the protection of participants, such as Serious Adverse Events, Unanticipated Problems, interim results, and protocol modifications. If this is not a multi-site study, state this.

**9. Study Administration**

**9.1 Intervention Assignment Methods**

*9.1.a* **Randomization**

**Describe procedures for generation, maintenance, and execution of the randomization schedule***, if applicable.*

*9.1.b***Blinding**

**Describe the procedure for maintaining the study blind for participants, investigators, and trial personnel***, if applicable.*

*9.1.c* **Unblinding**

**Describe the procedures for unblinding of study personnel during the conduct of the study***, if applicable*:

**9.2 Data Collection and Management and Confidentiality**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

* **Describe the system for maintaining primary records (source documents), case report forms, screening data (both for participants 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.**
* Address how the confidentiality of the data be ensured, from abstraction though analysis. Provide a specific plan for removing identifiers that meets the needs of the study and potential future uses of the data.
* Include a statement that all data and records generated during this study will be kept confidential in accordance with institutional policies, HIPAA on participant privacy, and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study or describe how the data may be shared.
* Describe the safeguards to maintain participant confidentiality.

**9.3 Data and Safety Monitoring Plan**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

* **Describe the data safety and monitoring plan (DSMP**).
* Include the processes and safeguards that will be in place to identify risks to research participants and to protect participants during the execution of the trial. The plan should be tailored to the risks of the study intervention, 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 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.

**9.4 Risk Assessment**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

* **Describe the risks of each research intervention or procedure in terms of magnitude and probability of harm.** Risks categories are:
* not greater than minimal
* a minor increase above minimal
* greater than minimal.
* Consider all physical, psychological, economic, or societal harms that might accrue to participants or others. Possible descriptions to include:
* Do certain subpopulations face greater risk or potential benefit than others? If so, how, and why?
* What measures are the study taking to minimize burden and risk, and ensure protections for those most vulnerable, understudied, or underrepresented?
* Does the study have the potential to influence health equity or disparities among individuals, communities, or other groups?
* As applicable, include potential risk by demographic subgroups.
* In addition, factors relating to social determinants of health (SDOH) may need to be listed with potential mitigation strategies for risk reduction.
* 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.

**9.5 Potential Benefits of Trial Participation**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**Summarize all potential benefits**, as applicable. Benefits should be broken down into direct benefits (i.e. accrue to the study participant as a result of participation) and indirect benefits (i.e. benefits that accrue to the individual or society in the future).

**9.6 Risk-Benefit Assessment**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**Include the justification for the Risk-Benefit for proceeding with the trial based on the balance between risks and benefits.**

**10. Informed Consent**

This information is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**10.1. 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.

**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.).

**10.2 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 the CHeRP SmartForm request a waiver of documentation of consent (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

**10.3 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, 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.).

**10.4 Adults with Impaired Decision-Making Capacity**

**Describe the process to determine whether an individual is capable of consent and who will make this assessment.** This process should reflect the complexity and risk level of the study.

**Describe the consent process for individuals with impaired decision-making capacity who are capable of consent. This may include special efforts made to accommodate their level of understanding**

**11. Publication**

The information in this section is also included in the CHeRP SmartForms, so please ensure it is consistent with the information in the SmartForm.

**Describe the plans for publication.**

*If applicable:* Include plans for dissemination of research findings to participants/community.

**12. References**

**Include all references in this section.**

**13. Appendix**

**Append relevant information.**