**NOTE:**

This is a template.

Please adjust to suit research project.

**Template Version: April 22, 2020**

**Protocol Template: Prospective Observational Study**

**PREFACE**

Remove this **Preface** before finalizing and distributing the Prospective Observational study protocol. This protocol template should be used for investigators conducting prospective observational research studies, specifically cohort, case-control, cross-sectional, descriptive, and educational initiatives / interventions (i.e., clinical simulation).

The goal of this template is to assist you in writing a comprehensive prospective observational protocol*.* Its use will help you think through the scientific basis of your assumptions, minimize uncertainty in the interpretation of outcomes, and prevent loss of data.

**INSTRUCTIONS ON HOW TO USE THIS TEMPLATE**

The template includes the framework for organizing your protocol, as well as instructions and example text.

*Italics:* **Instruction / Explanatory Text** is indicated by *italics.* This text provides information on the content that should be included; these instructions should be deleted once you complete a section. Footnotes to instructional text should also be deleted. The instructions also note if a section should be left blank.

[Regular font]: **Example Text** is indicated in [regular font]. Within example text, the need to insert specific information is notated by <angle brackets>. Example text is included to further aid in protocol writing and should either be modified to suit the study, objectives and / or design. If not applicable for your study, delete the example text.

You will find it helpful to consider all sections, however, depending on your research focus and design, not all sections will be applicable to your study and you should delete sections (including the section heading) that do not apply.

If sections are deleted, ensure that any text that refers to another section is updated as needed. The section headers include formatting to generate a table of contents. Once the protocol is written, ensure the table of contents is updated (right click on the table of contents and select ‘Update Field’) to reflect any changes.

Version control is important to track protocol development, revisions, and amendments. It is also necessary to ensure that the correct version of a protocol is used by all staff conducting the study. With each revision, the version date located in the header of each page should be updated.

**RESOURCES**

Remove **Resources** before finalizing and distributing the prospective observational protocol.

* [SickKids Clinical Research Services](about:blank)
* SPRINT: Streamlined Pathway for Research Initiation
* **Consent for Non-Interventional/Observational Studies - Parent**(v.Nov 2019)
* [**Prospective Studies Main Application Checklist**](about:blank)(v.Apr 2019)

**<tITLE OF THE PROTOCOL>**

|  |  |
| --- | --- |
| **Principal Investigator:** | *Insert the Name of the Investigator*  *Insert Department Name*  *Insert Address*  *Insert Email Address*  *Insert Phone Number* |
| **Additional Investigators:**  *[PI at additional sites, etc. as applicable]* | *Insert the Name of the Investigator*  *Insert Department Name*  *Insert Address*  *Insert Email Address*  *Insert Phone Number* |
| **Sponsor:** | *Insert Sponsor* |
| **Funding by:** *[If applicable]* | *Insert Funding Source (e.g., CIHR, Heart and Stroke Foundation, MOHLTC, etc.)* |
| **Version Date [Day, Month, Year]** | *All versions must have a date. Version date must be updated with each amendment. Use the international date format (day month year) and write out the month (e.g., 24 May 2020).* |

**Statement of Compliance**

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Research Ethics Board (REB) of Record, except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB of Record for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol or consent materials will require review and approval by the REB of Record before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

*This page should be signed by the Principal Investigator at each site. If this is a single center study conducted only at SickKids, delete the site address below.*

Principal Investigator:

Name:

Signed: Date: This name line indicates where a Principal Investigator would enter their name. 

<DD Month YYYY>

Site Address

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Table of Contents**

1 PROTOCOL SUMMARY 1

1.1 Synopsis 1

1.2 Schematic of Study Design 2

1.3 Schedule of Activities (SOA) 3

1.4 Key Roles 3

2 Introduction, Background Information and Scientific Rationale 4

2.1 Background Information and Relevant Literature 4

2.2 Rationale 4

2.3 Potential Risks & Benefits 4

2.3.1 Potential Risks 4

2.3.2 Potential Benefits 4

3 Objectives and Purpose 5

3.1 Primary Objective 5

3.2 Secondary Objectives (if applicable) 6

4 Study Design and Endpoints 6

4.1 Description of Study Design 6

4.2 Duration of Study Participation 7

4.3 Total Number of Participants and Sites 7

5 Study Enrollment and Withdrawal 7

5.1 Participant Inclusion Criteria 7

5.2 Participant Exclusion Criteria 8

5.3 Strategies for Recruitment and Retention 8

5.4 Participant Withdrawal or Termination 9

5.4.1 Reasons for Withdrawal or Termination 9

5.4.2 Handling of Participant Withdrawals or Termination 10

6 Study Assessments and Procedures 10

7 Study Procedures / Evaluations 10

7.1 Procedures / Evaluations 10

7.2 Laboratory Procedures / Evaluations 10

7.3 Study Specific Biospecimens 11

7.3.1 Specimen Collection Procedures 11

7.3.2 Specimen Preparation, Handling, and Storage 11

7.3.3 Specimen Shipment 11

7.4 Questionnaire Administration 11

8 Statistical Considerations 11

8.1 Study Hypotheses 12

8.2 Sample Size Determination 12

8.3 Statistical Methods 12

9Source Documents and Access to Source Data / Documents 12

10 Study Oversight 13

11 Ethics / Protection of Human Participants 13

11.1 Ethical Standard 13

11.2 Informed Consent Process and Documentation 13

11.3 Consent / Assent and Other Informational Documents Provided to Participants 14

12 Data Handling and Record Keeping 15

12.1 Data Collection and Management Responsibilities 15

12.2 Study Records Retention 15

13 Protocol Deviations 16

14 Publication and Data Sharing Policy 16

15 References 16

*Be sure to update the table of contents when you are finished creating your protocol. You can do this in Microsoft Word by going to the References tab and clicking on “Update Table” in the Table of Contents section.*

**List of Abbreviations**

*Add all disease or study-specific abbreviations/acronyms in this section. Modify this list as needed for your particular study and remove abbreviations that are not used in the document.*

|  |  |
| --- | --- |
| AE | Adverse Event/Adverse Experience |
| CRF | Case Report Form |
| CTU | Clinical Trial Unit |
| CRS | Clinical Research Services |
| PI | Principal Investigator |
| PHI | Personal Health Information |
| PHIPA | Personal Health Information Protection Act |
| REB | Research Ethics Board |
| SAEs | Serious Adverse Events |
| SOA | Schedule of Activities |
| TP | Treating Physician |

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

|  |  |
| --- | --- |
| Title | *Full title of protocol.* |
| Short Title | *Shortened title, if one is typically used by you or your Center / Dept.* |
| Study Description | *Provide a short overview of the protocol, study design, including sample size, study groups, schedule of interventions, schedule for specimen or data collection, and analyses to be performed.*  *This summary should be only a few sentences in length. A detailed schematic describing all visits and assessments (schedule of events) should be included in the Schematic of Study Design.* |
| Objectives | *Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol.* |
| Study Design | *Include an overview of the design.* |
| Participant Population, Selection Criteria | *Include the inclusion and exclusion criteria.* |
| Study Sites | *Insert a list of participating sites. If greater than 3 sites, indicate number of sites and refer to Section 1, Key Roles, for a complete list of participating sites.* |
| Participant Duration | *Time it will take for each individual participant to complete all participant observation(s).* |
| Number of participants | *Number of participants projected for the entire study (e.g. 100 participants expected to be enrolled across two sites).* |
| Study Phases (Screening, Study Treatment, Follow-Up) | *Usually observational studies have at least 2 phases: (1) Screening: screening for eligibility and obtaining consent; and (2) Observation Period: measurements made for monitoring participants once (cross-sectional) or over time (cohort).* |
| Efficacy Evaluations | *Evaluation measurements that will be used to assess the primary and secondary objectives.* |
| Safety Evaluations | *Primary measurements that will be used to assess safety.* |
| Statistical Analysis | *A very brief description of the main elements of the statistical methodology to be used in the study. Limit this section to discussion of the analysis of the primary objectives and perhaps the main secondary objectives.* |
| Data and Safety Monitoring Plan | *Describe who is responsible (i.e., Principal Investigator) for data quality management and ongoing assessment of the study conduct.* |

## 1.2 Schematic of Study Design

*The diagram below shows a sample format and the level of detail needed to convey an overview of a study design. Complete each text box with study-specific information and adapt the diagram to illustrate your respective study design. The time point(s) indicated in the schematic should correspond to the time point(s) in Section 7 of the protocol, Study Procedures / Evaluations, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.*

Total N: Obtain informed consent. Screen potential participants by selection criteria; obtain history, document.

Prior to

Enrollment

Perform Initial Assessments

(List specimens to be collected, examinations, imaging or laboratory assays to be performed, and questionnaires to be completed)

Visit 1

Time Point

Visit 2

Follow-up Assessments

(List specimens to be collected, examinations, imaging or laboratory assays to be performed, and questionnaires to be completed)

Time Point

Follow-up Assessments

(List specimens to be collected, examinations, imaging or laboratory assays to be performed, and questionnaires to be completed)

**Visit** 3

Time Point

Visit X

**Final Assessments**

List analyses to be performed

Time Point…

## 1.3 Schedule of Activities (SOA)

*The schedule of activities must capture the procedures at each study visit, and all contact, with study participants (e.g., telephone contacts). Do not add unnecessary procedures to the study; procedures should contribute to participant eligibility, study objectives and endpoints or for compliance and safety evaluations.*

*When planning study procedures, be clear as to which procedures are being conducted and when. This has an impact on the study budget and billing. Consider adding a footnote to identify all procedures that are part of standard of care.*

*Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the visit time points to study endpoints.*

***The schedule below is as an example and should be modified as appropriate to reflect the study design, visit schedule and procedures.***

[Guidance and example use noted in blue]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Activity** | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] |
| **Study team procedures** |  |  |  |  |  |  |
| Informed Consent | X |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |
| Physical Exam | X | X | X | X | X | X |
| Vitals signs | X | X | X | X | X | X |
| Participant Survey | X |  | X |  |  | X |
| ***Cardiology assessments*** |  |  |  |  |  |  |
| Electrocardiogram | X |  | X |  |  | X |
| Doppler flow echo cardiogram | X |  | X |  |  | X |
| ***Laboratory Assessments*** |  |  |  |  |  |  |
| Chemistry panel | X | X | X | X | X | X |
| AST and ALT | X | X | X | X | X | X |
| ***Imaging Assessments*** |  |  |  |  |  |  |
| Chest X-ray | X |  | X |  |  | X |

## 1.4 Key Roles

<Insert Text>

*Provide a list of the persons, and / or groups serving in key roles in the conduct or oversight of the study. This should include the PI and site investigators.*

*Include the following information for each investigator:*

*Name, degree, title*

*Institution Name*

*Address*

*Phone Number*

*Email*

# Introduction, Background Information and Scientific Rationale

## 2.1 Background Information and Relevant Literature

<Insert Text>

*This section should contain a background discussion of the condition to be observed. Include the following:*

* *The name and description of the health problem that the study will observe.*
* *Discussion of important literature (i.e., clinical, epidemiological and / or public health) and pediatric data that are relevant to the study that provide background for the study (reference citations should be listed in Section 15, References).*
* *A brief discussion of the study’s overall goal.*
* *Importance of the study and any relevant treatment issues or controversies.*

## Rationale

<Insert Text>

*State the problem or question under study (e.g., describe the disease and current limitations of knowledge or therapy). Include a statement of the hypothesis. Include a justification for the selection of study population. Describe the rationale for the type and selection of control (e.g. no treatment or historical). Discuss known or potential problems associated with the control arm chosen in light of the specific disease being studied.*

## Potential Risks & Benefits

### Potential Risks

<Insert Text>

*Include a discussion of known potential risks, e.g. risk of breach of confidentiality. Relevant published literature that may provide relevant risk information. Describe in detail any psychological, social, legal, economic, or any other risks to participants by virtue of participation in the study that the PI foresees, addressing each of the following:*

* *Immediate risks*
* *Long-range risks*
* *Rationale for the necessity of exposing human participants to such risks.*
* *Why the value of the information to be gained outweighs the risks involved?*

### Potential Benefits

<Insert Text>

*Include a discussion of known potential benefits from either clinical or nonclinical studies. Published literature may provide potential and relevant information.*

*Describe, in detail, any potential benefits to participants or society that the PI foresees, addressing each of the following:*

* *Immediate potential benefits*
* *Long-range potential benefits*

*Note: Payment to participants, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a “benefit.” Provision of incidental care is also not to be considered a benefit.*

# Objectives and Purpose

<Insert Text>

*Provide a detailed description of the primary objective(s) and any secondary objective(s) of the study. An objective is the reason for performing the study in terms of the scientific question to be answered. The primary objective is the main question. Also, the primary objective generally drives statistical planning for the study (e.g., calculation of the sample size to provide the appropriate power for statistical testing).*

Note: Do not include statistical analysis here. Secondary objectives are goals that will provide further information on the health condition that is the focus of the study.

*Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general or specific purpose, e.g., to evaluate biomarkers as physiologic correlates of disease, to determine risk factors for disease or condition, etc.*

## Primary Objective

<Insert Text>

*Specify the primary outcome measures of this study. In the tables, give precise definitions of the outcome measures used to address the study’s primary objective(s).*

|  |  |  |  |
| --- | --- | --- | --- |
| **Objective** | **Brief Description / Justification of Outcome Measure** | **Outcome Measured By** | **Time Frame** |
| <Insert text>  {The primary objective is the main question. This objective generally drives statistical planning for the study (e.g., calculation of the sample size to provide the appropriate power for statistical testing).} | <Insert text>  {Briefly explain why the outcome measure was chosen. The primary outcome measure’s importance and role in the analysis and interpretation of study results should be clear. The primary outcome(s) is the basis for concluding that the study met its objective. Generally, there should be just one primary outcome that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary outcomes may require an adjustment to the sample size calculations and p-value threshold.} | <Insert text>  {Briefly state how the primary outcome measure will be assessed (e.g., instrument name, biomarker assay, radiograph).} | <Insert text>  {Include the study visits or time points at which each primary outcome measure will be assessed.} |

## Secondary Objectives (if applicable)

<Insert Text>

*Specify any secondary outcome measures, i.e., the measurements or observations used to describe the patterns of diseases, traits or associations with exposures, risk factors, and / or treatment. Include the study visits at which the biospecimens, images or other data will be obtained and the specific laboratory tests or other analytical measures to be used.*

*Outcome measures should be prioritized and should correspond to the study objectives and hypotheses being tested.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Objective** | **Brief Description/Justification of Outcome Measure** | **Outcome Measured By** | **Time Frame** |
| <Insert text>  {Briefly state the secondary objective(s). The secondary objective(s) are goals that will provide further information on the health condition that is the focus of the study.} | <Insert text>  {Briefly explain why the outcome measure was chosen. It is recommended that the list of secondary outcome measures be short, because the chance of demonstrating an effect on any secondary outcome measures after appropriate correction for multiplicity becomes increasingly small as the number of endpoints increases.} | <Insert text>  {Briefly state how the secondary outcome measure(s) will be assessed (e.g., instrument name, biomarker assay, radiograph).} | <Insert text>  {Include the study visits or time points at which each secondary outcome measure will be assessed.} |
| <Insert text> | <Insert text> | <Insert text> | <Insert text> |

Note: Delete tables that do not apply (i.e., secondary outcomes).

# Study Design and Endpoints

## Description of Study Design

<Insert Text>

Include a brief paragraph or bulleted text describing the study design. This section should include:

* A brief description of the type / design of study to be conducted [e.g., cross-sectional, cohort, case-control, case-only, case-crossover, ecological or community study, or other]; state if it is a multicenter study.
* A brief description of the study population (e.g., health status, inpatient / outpatient, demographic groups), sample size and characteristics of different study groups, if applicable. Do not list selection criteria here, as these will be listed in Sections 5.1 and 5.2.
* A brief discussion of the rationale for design features.
* A brief description of the study timeline, including approximate time to complete enrollment and expected duration of participant’s participation (details of study visit schedule will be included in Section 7, Study Procedures / Evaluations).
* A brief summary of data collection methods for the assessment of study objectives (detailed methods will be included in Section 7, Study Procedures / Evaluations).
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical images).
* If the study requires that study staff (investigator, examiner, laboratory personnel, etc.) be masked with respect to the study group of a research participant, specimen, or image, state how masking will be maintained.

## Duration of Study Participation

<Insert Text>

*This refers to the duration of the study participants’ participation and not simply the duration of the study. This should include screening, observational phase, and any follow up time period.*

## Total Number of Participants and Sites

<Insert Text>

*Include the number of participants that will be enrolled at SickKids and the number of participants that will be enrolled elsewhere, if applicable.*

*{Begin sample text}*

Recruitment will end when approximately \_\_\_ participants are enrolled. It is expected that approximately \_\_\_ participants will be enrolled in order to produce \_\_\_ evaluable participants.

*{End sample text}*

# Study Enrollment and Withdrawal

*The following subsections should include a description of the study population, participant recruitment, and issues related to participant withdrawal. The study population should be appropriate for the stage of the study.*

*Use the following guidelines when developing participant eligibility criteria to be listed in Sections 5.1 Participant Inclusion Criteria and 5.2 Participant Exclusion Criteria:*

* *The eligibility criteria should provide a definition of participant characteristics required for study entry / enrollment.*
* *If participants require screening, distinguish between screening participants vs. enrolling participants. Determine if screening procedures will be performed under a separate screening consent form.*
* *The same criterion should not be listed as both an inclusion and exclusion criterion (e.g., do not state age >18 years old as an inclusion criterion and age ≤ 18 years as an exclusion criterion).*
* *Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.*

## Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

<Insert Text>

Inclusion criteria are characteristics that define the population under study, e.g., those criteria that every potential participant must satisfy, to qualify for study entry. Provide a statement that individuals must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion.

*Create a numbered list of criteria that an individual must meet to be eligible to participate in the study.*

*Some criteria to consider for inclusion are provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, gender, health status, diagnosis or symptoms, background medical treatment, and laboratory ranges. Additional criteria should be included as appropriate for the study design and risk.*

[In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Consent provided
2. Aged <specify range>
3. In good general health as evidenced by medical history OR Diagnosed with <specify condition/disease> OR Exhibiting <specify clinical signs or symptoms or physical/oral examination findings>
4. <Specify laboratory test> results between <specify range>]

## 5.2 Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

<Insert Text>

Exclusion criteria are characteristics that make an individual ineligible for study participation. Provide a statement that all individuals meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion. Limited English proficiency cannot be an exclusion criterion.

*Create a numbered list of criteria that would exclude an individual from study enrollment. Some criteria to consider for exclusion are pre-existing conditions or concurrent diagnoses, concomitant use of medication(s) or devices, other factors that would cause harm or increased risk to the participant or close contacts or preclude the participant’s full adherence with or completion of the study. Additional criteria should be included as appropriate for the study design and risk.*

## Strategies for Recruitment and Retention

<Insert Text>

*Identify strategies for participant recruitment and retention,* *e.g. from investigator or sub-investigator clinical practices, referring physicians, advertisement, EPIC, etc.*

*Include details as to whether or not the recruitment plan proposes to use any SickKids media services (communications, marketing, etc.) and social media (e.g., Facebook, Twitter, etc.). Note: All recruitment materials which will be seen by potential participants need to be approved by the REB.*

*Describe how participants will be identified and recruited for the study. The identification of participants must protect their privacy. Privacy refers to individuals and their interest in controlling the access of others to themselves. Include the following:*

* *The time and place where informed consent will take place.*
* *The nature of the information participants will be asked to give about themselves.*
* *Who receives and can use the information?*

*For example, individuals might not want to be seen entering a place that might stigmatize them, such as a pregnancy-counseling center that is clearly identified as such by signs on the front of the building.*

*If you are using EPIC information for recruitment purposes, discuss:*

* *How the data will be gathered from EPIC.*
* *How the data will be used (be specific regarding the purpose e.g. participant identification, informing participants, initial discussion of participant eligibility, etc.)?*
* *All data points and Personal Health Information (PHI) that will be used for the search.*
* *When the data will be discarded after use and how the data will be discarded.*
* *Parameters (how many times the study team will search EPIC over the course of the study and / or how often queries regarding eligible participants will run during the course of the study).*
* *The method used to notify the treating physician (if any, and if no explain why)?*
* *A description of how the potential participant will be contacted (email, phone, text, mailed letters etc.).*

*If the study requires long-term participant participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance).*

*In addition, consider inclusion of the following information:*

* *Target sample size; identify anticipated number to be screened in order to reach the target enrollment (should be consistent with information contained in Section 8.2, Sample Size Determination);*
* *Anticipated accrual rate;*
* *Source of participants (e.g., inpatient hospital setting, outpatient clinics, student health service, or general public);*
* *Recruitment venues;*
* *How potential participants will be identified and approached;*
* *Type of advertisements planned (e.g. national newspaper, local flyers; specific names are not needed), and a statement that any advertisements must be approved by the REB for the site.*
* *If participants will be compensated for study participation, describe amount and schedule of payments.*
* *If the study requires long-term participation, describe procedures that will be used to enhance retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance, etc.).*
* *Describe the plans to minimize loss to follow-up and missing data. The description should include when a participant will be considered lost to follow-up (e.g., if he or she fails to return for specified number of scheduled visits and is unable to be contacted by the study site staff) and whether the study design will accommodate replacing lost/withdrawn participants.*

## Participant Withdrawal or Termination

### Reasons for Withdrawal or Termination

<Insert Text>

*Provide a list of reasons for the termination or withdrawal of a participant (e.g. safety reasons, failure of participant to adhere to protocol requirements, participant consent withdrawal, disease progression, etc.). It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also note that participants may withdraw voluntarily from the study at any time.*

*{Begin sample text}*

Participants are free to withdraw from taking part in the study at any time upon request. An investigator may terminate participation in the study if:

* Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
* The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

*{End sample text}*

### Handling of Participant Withdrawals or Termination

<Insert Text>

*Describe efforts that will be made to continue follow-up of withdrawn or terminated participants, if applicable. If a participant withdraws consent to participate in the study, describe whether attempts will be made to obtain permission to record at least survival data up to the protocol-described end of participant follow-up period. Also specify the methods that should be used before a participant is considered lost to follow-up (e.g. number of phone calls to participant, phone calls to next-of-kin if possible, certified letters, etc.).*

*This section should include a discussion of replacement of participants who withdraw or discontinue early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in Section 8, Statistical Considerations.*

# Study Assessments and Procedures

<Insert text>

Include any evaluations necessary to assess whether an individual meets the eligibility criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the time frame prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment).

This section must include instructions for obtaining signed informed consent. If procedures are required for confirmation of eligibility (e.g., review of medical records, clinical examination or laboratory tests) describe the process and indicate if any additional consenting is needed for the pre-screening procedures.

Confirm that the procedures listed are consistent with those included in the Schedule of Activities (Section 1.3).

# Study Procedures / Evaluations

*In the following subsections, describe procedures for collection of all study data including clinical observations, laboratory results, biospecimens, images, and questionnaire responses. Information outlined in this section should refer to and be consistent with the information in the Schedule of Activities (Section 1.3).*

*Procedures completed during the study as part of normal standard of clinical care should be identified as such.*

## Procedures / Evaluations

<Insert text>

Describe assessments to be done, such as baseline medical history, medications history, radiographs or photographs, and other health status evaluations.

## Laboratory Procedures / Evaluations

<Insert text>

List all laboratory evaluations. Differentiate screening laboratories from evaluations required for study outcomes. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-comparison (e.g., use of consistent laboratory method throughout study). If more than one laboratory will be used, specify which evaluations will be done by each laboratory.

## Study Specific Biospecimens

### Specimen Collection Procedures

<Insert text>

Specify what specimens will be collected specifically for the study and the general procedures for the collection. If specimen collection procedures are complex, the protocol should include only a general description.

* Specimen source – Describe how the biospecimens will be obtained, e.g., from a biorepository.

### Specimen Preparation, Handling, and Storage

<Insert text>

Describe where and how the specimens are processed after collection. Explain any special instructions for the preparation, handling, and storage of specimens. Include required temperatures for immediate and long-term storage, procedures for aliquoting specimens, where specimens will be stored, how they will be labeled and tracked for inventory, and measures taken to ensure sample integrity during storage. Include a discussion of long-term access and consent for future use of specimens.

### Specimen Shipment

<Insert text>

If specimens will be shipped to another location for analysis or storage, identify the receiver and provide destination and shipment information, including shipping frequency. Include here the contact information for laboratory personnel, days and times shipments are allowed, and any labeling requirements for specimen shipping. Also, include any special instructions such as dry ice or wet ice or the completion of a specimen-tracking log. Indicate how specimens will be labeled for tracking purposes and whether labels include participants’ identifying information. Provide information on the general mode of shipment and measures taken to protect specimen integrity.

## Questionnaire Administration

<Insert text>

If questionnaire completion is required, describe the purpose and content of the questionnaire. Specify by whom and how the questionnaire will be administered and who will be the respondents. State whether the questionnaire has been previously validated.

# Statistical Considerations

*The following subsections should describe the statistical tests and analysis plans for the protocol. A description of how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible should be provided. The statistical section should describe this approach, including frequency reporting of variables, confidence intervals, etc.*

*Consult with a statistician when completing Section 8. Support is available through:*

*a) The Clinical Trial Unit (CTU):* [*http://my.sickkids.ca/research/clinical-research-services/clinical-trials-roadmap/Pages/Development.aspx*](about:blank)

*b) Clinical Research Services (CRS)*

[*http://my.sickkids.ca/research/clinical-research-services/Pages/default.aspx*](about:blank)*)*

## 8.1 Study Hypotheses

<Insert text>

## 8.2 Sample Size Determination

<Insert text>

Provide all information needed to validate your calculations.

Consider applicable items from the following list when describing sample size determination:

* Statistical method used to calculate the sample size
* Outcome measure used for calculations (almost always the primary variable)
* Test statistic
* Type I error rate
* Type II error rate
* Method for adjusting calculations for planned interim analyses, if any.
* Assumptions used in calculations:
  + Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome), justified and referenced by historical data as much as possible.
  + Assumed dropout rates, withdrawal, missing data, etc., also justified.
  + Approach to handling withdrawals and protocol violations, i.e., to what extent data from withdrawn participants will be evaluable, whether withdrawn participants will be replaced.

Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size. Most assumptions are not accurate as point estimates.

Discuss whether the sample size also provides sufficient power for addressing secondary objectives or for secondary analyses in key subgroup populations.

## 8.3 Statistical Methods

<Insert text>

*Describe analyses for assessing the primary and secondary objectives. Plans must clearly identify the analyses, data stratifications, and methods to account for missing, unused or spurious data. Discuss how outcome measures will be assessed and transformed, if relevant, before analysis (e.g., is the primary variable binary, categorical, or continuous?).*

*For complex data analyses (e.g., multiple secondary objectives), an overview of the statistical analyses may be provided here, with more details in a separate statistical analysis plan written prior to performing any analyses. This section should contain the key elements of the analysis plan, but does not need to be a full reiteration of a detailed study analysis plan created by the study biostatistician.*

# 9Source Documents and Access to Source Data / Documents

<Insert Text>

*Each participating site will maintain appropriate medical and research records for this study, in compliance with institutional requirements for the protection of confidentiality of participants. Describe in this section who will have access to records.*

*Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants’ memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the study.*

*{Begin suggested text}*

Access to study records will be limited to REB-approved members of the study team. The PI will permit study-related monitoring, audits, and inspections by the REB and / or University compliance and quality assurance groups of all study related documents (e.g. source documents, data collection instruments, study data etc.). The PI will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as a PI in this study implies acceptance of potential inspection by REB and / or applicable University compliance and quality assurance offices.

*{End suggested text}*

# Study Oversight

*Describe the safety and monitoring plan. Indicate who is responsible for data safety monitoring of the overall study and what are his / her / their credentials, what events / data points will be reviewed during data safety monitoring reviews, what is the frequency of data safety monitoring reviews, a description of predefined stopping rules for the entire study, if applicable, and how reports/decisions following data safety monitoring reviews will be disseminated to sites (if it is a multicenter study with SickKids as the main site).*

# Ethics / Protection of Human Participants

## Ethical Standard

<Insert Text>

*Include in this section the guiding ethical principles being followed by the study.*

## Informed Consent Process and Documentation

<Insert Text>

*Describe how informed consent will be administered. Describe who will obtain consent (using roles, note names) and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the participant / participant’s legally authorized representative. Include information such as:*

* *Where the consent process will take place.*
* *How participant privacy will be assured.*
* *Whether participants will be permitted to provide consent at the time of the consent discussion or whether they will be required to come back to provide written informed consent.*
* *How the PI will ensure that participants comprehend the nature of the study.*
* *Steps that will be taken to avoid coercion.*

*If the protocol involves multiple consenting sessions, or multiple informed consent forms, describe this information and the associated procedures in detail. If a sample informed consent form is provided in an appendix to the protocol, state so here.*

*Describe any proposed waivers or alterations to informed consent. Describe any special circumstances regarding obtaining consent. Describe plans for obtaining consent from speakers of language other than English.*

*If not all participants will have the capacity to give informed consent, describe how capacity will be assessed. Describe the anticipated degree of impairment relative to their ability to consent to participate in research. Research with persons who have diminished capacity is allowed only for minimal risk or direct benefit studies.* *Clearly document that the PI has an adequate plan in place to assure an acceptable level of comprehension before consent is obtained. If children will be participants, include a specific plan to assess comprehension during assent (the participant’s agreement).*

*The PI is responsible for ensuring that valid consent is obtained and documented for all participants. Specifically describe how consent will be documented and how / where documentation will be stored.*

*{Begin sample text}*

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be REB approved and the potential participant will be asked to read and review the document. The PI will explain the research study to the potential participant and answer any questions that may arise. All potential participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Potential participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The potential participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The potential participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the participant’s research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the participant’s research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

*{End sample text}*

## Consent / Assent and Other Informational Documents Provided to Participants

<Insert Text>

*This section should demonstrate that the consent form contains all required elements. List all consent documents and materials submitted with this protocol. Include consent and / or assent forms, printed or web-based materials, phone scripts and any other related material.*

*If needed, describe special documents or materials (e.g., Braille, another language, audio recording) and if assent was originally obtained from participants, a regular re-assessment of capacity should be completed as the child matures and consent will be obtained as soon as the child reaches capacity to consent for their own participation (if applicable).*

*{Begin sample text}*

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant. Written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol <insert list>.

*{End sample text}*

# Data Handling and Record Keeping

*The following subsections should include a description of the data handling and record keeping for the conduct of the study.*

## Data Collection and Management Responsibilities

<Insert Text>

*Provide details regarding the type(s) of data captured that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Briefly describe steps to be taken to ensure that the data collected are accurate, consistent, complete, and reliable.*

*Describe responsibilities for data handling and record keeping. Information should include the role in data collection, review of data, study materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes, if applicable.*

*If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.*

*Indicate the roles of each party with regards to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.*

*{Begin sample text}*

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant’s official electronic study record.

Clinical data and clinical laboratory data will be entered into <specify name of data capture system>, a data capture system provided by the <specify DCC>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Study data will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at The Hospital for Sick Children. The application and data are housed on servers provided by The Hospital for Sick Children. These servers are located within SickKids secure data center. Local support for REDcap is provided by SickKids Research IT.]

*{End sample text}*

## Study Records Retention

<Insert Text>

*Specify the length of time for the PI to maintain all records pertaining to this study. The PI should use the most conservative rule for document retention – i.e., retention should follow the rule that has the longest period.*

# 13 Protocol Deviations

<Insert Text>

*Plans for detecting, reviewing, and reporting deviations from the protocol should be described. A statement should be included to indicate that deviations are not allowed unless a statement is included in the investigator agreement. Provisions for approval of deviations can be described.*

# 14 Publication and Data Sharing Policy

<Insert Text>

*The publication and authorship policies should be established and clearly outlined in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Refer to your specific contract grant and / or Study Agreements.*

# References

*This is the bibliography section for any information cited in the protocol. It should be organized as any standard bibliography.*

1. Author, Title of work, periodical and associated information.
2. Author, Title of work, periodical and associated information.