**PREFACE**

Remove this **Preface** before finalizing and distributing the clinical trial protocol.

As part of the protocol development process, ensure that adequate consideration has been made to the feasibility, validity, resources and budget. By seeking advice from other experts (e.g., biostatisticians, methodologist, health economist, pharmacists, etc.) at the stage of protocol development, you will maximize the chances for success.

The goal of this template is to assist you in writing a comprehensive clinical trial protocol that meets the standard outlined in the *International* *Council on Harmonisation (ICH) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (GCP) E6(R2).* 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. The template has been modified from the NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template to reflect Canadian and SickKids language.

**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 intervention (e.g. drug, biological, natural health product or device), design, and conduct of the planned clinical trial or, if not appropriate for your study, delete the example text.

You will find it helpful to consider all sections, however, depending on your research area and trial design, not all sections will be applicable to your trials 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 (refer to Section x.y) 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 trial. With each revision, the version date located in the header of each page should be updated.

**RESOURCES**

Remove **Resources** before finalizing and distributing the clinical trial protocol.

* [SickKids Clinical Research Services](http://my.sickkids.ca/research/clinical-research-services/Pages/default.aspx)
* [SPRINT: Streamlined Pathway for Research Initiation](http://my.sickkids.ca/research/clinical-research-services/Pages/CRAIC.aspx)

International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

* [ICH Harmonised Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice: E6(R2](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf))
* [ICH Harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports: E3](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf)
* [ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials: E9](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf)
* [Final Concept Paper E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9__R1__Final_Concept_Paper_October_23_2014.pdf)
* [ICH Harmonised Guideline, Addendum to ICH E11: Clinical Investigation of Medicinal Projects in the Pediatric Population: E11(R1)](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf)

Health Canada

* [Food and Drugs Act and Regulations, Part C, Division 5: Drugs for Clinical Trials Involving Human Subjects](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/links.html)
* [Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html)
* [Biologics, Radiopharmaceuticals and Genetic Therapies](https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies.html)
* [Natural Health Products Regulations: Part 4 Clinical Trials Involving Human Subjects](http://laws-lois.justice.gc.ca/eng/regulations/SOR-2003-196/)
* [Medical Devices Regulations: Part 3 – Medical Devices for Investigational Testing Involving Human Subjects](http://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/index.html)

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)

* [TCPS2](http://www.pre.ethics.gc.ca/eng/archives/tcps2-eptc2-2010/Default/)
* [TCPS2 Online Tutorial](http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel)

Personal Health Information Protection Act (PHIPA)

* [PHIPA](https://www.ontario.ca/laws/statute/04p03)

Other

* [SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)](http://www.spirit-statement.org/)
* [Citing Medicine, 2nd edition: The NLM Style Guide for Authors, Editors, and Publishers](http://www.ncbi.nlm.nih.gov/books/NBK7256/)
* [CONSORT statement](http://www.consort-statement.org/)
* [International Committee of Medical Journal Editors (ICMJE): Recommendations](http://www.icmje.org/recommendations/)

**<Title>**

*The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity and neutrality is the goal. If there is a “short title” (e.g., an abbreviation used to refer to the study title), also include it here and it can be used throughout this document in place of the full title.*

**Protocol Number: < Number>**

*Protocol number may be assigned by a Sponsor or consortium (otherwise delete).*

**Principal Investigator:** **< Name Principal Investigator>**

**Sponsor: <Sponsor name, if applicable>**

*Sponsor means an individual, pharmaceutical or medical device company, governmental agency, academic institution, private organization, or other organization who takes responsibility for and initiates a clinical investigation. For SickKids Investigator Initiated trials, this should read as* ***Dr. <PI name> and The Hospital for Sick Children****.*

**Funded by: < Insert Funding Source (e.g., CIHR, PSI, 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., 23 June 2017).*

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# STATEMENT OF COMPLIANCE

*Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements. Each engaged institution must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Research Ethics Board (REB) or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before implementation. Update the statement below as applicable. 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.*

The trial will be conducted in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements. 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), except where necessary to eliminate (an) immediate hazard(s) to the trial participants.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB 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 will require review and approval by the REB 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.

Name of Principal Investigator (Print): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Signature of Principal Investigator: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_

<DD Month YYYY>

Site Address

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# PROTOCOL SUMMARY

## Synopsis

|  |  |
| --- | --- |
| **Title:** | <Full title> |
| **Study Description:** | *Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length.*  *Include details such as single-/multi-centered, double-blinded, randomized, the intervention being tested, the disease or behaviour being studied, etc.. If the study is a comparison of an experimental intervention versus the standard of care, ensure this is clear as this may have regulatory implications.* |
| **Objectives:** | *Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol.*  <Primary Objective:  Secondary Objectives:  Exploratory Objectives: > |
| **Endpoints:** | *Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol.*  <Primary Endpoint:  Secondary Endpoints:  Exploratory Endpoints: > |
| **Study Population:** | *Specify the sample size, gender, age, demographic group, general health status and any other key factors.* |
| **Phase:** | *<1, 2 or 3, 4 or N/A> Phase applies to drugs and biologics. Refer to the* [glossary](http://my.sickkids.ca/research/clinical-research-services/Pages/Glossary.aspx) *for more information on phases. For Phase 1 trials, contact Clinical Research Services at* [aSK.CRS@sickkids.ca](mailto:aSK.CRS@sickkids.ca) *for additional resources.* |
| **Description of Study Intervention:** | *Describe the study intervention. If the study intervention is a drug, biological or natural health product, include dose and route of administration. For devices, provide a brief description of the device.* |
| **Study Duration:** | *Estimated time (in months) from when the study opens to enrollment until completion of data analyses.* |
| **Participant Duration:** | *Time (e.g., in months) it will take for each individual participant to complete all participant visits.* |

## Schema

*This section should include a diagram that provides a quick “snapshot” of the study and ideally be limited to 1 page. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). If a study arm represents the standard of care, include this in the schematic. The time point(s) indicated in the schematic should correspond to the time point(s) in* ***Section 1.3,******Schedule of Activities****, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.*

***Example #1 provided as a guide, customize as needed: Flow diagram***

Prior to

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

Enrollment

Randomize

Perform baseline assessments.

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Administer initial study intervention.

Visit 1

Time Point

<week/day>

Visit 2

Repeat study intervention (*if applicable*).

Time Point

<week/day>

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Visit 3

Time Point

<week/day>

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Visit 4

Time Point

<week/day>

**Final Assessments**

<list analyses to be performed OR refer to **Section 1.3, Schedule of Activities**>

Visit X

Time Point

***Example #2*** ***provided as a guide, customize as needed: Timeline diagram***

Day -7 to Day -1

Screening

Day 1

Randomization

Week 1

Titration

Weeks 2 - 25

Maintenance

Week 26

Dose Taper

Week 27

End of Study Assessments (EOS)

Week 28-29

Follow-up Phone Call

Study Intervention N=

Placebo N=

# in-clinic visits and

# telephone contacts

<Insert schematic>

## 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. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. 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 occurring as standard of care (and the data will be used for the study) versus procedures that are being done exclusively for study purposes. 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 (e.g., pharmacokinetic (PK) studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks) and if the visits align with clinical visits.*

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

| **Procedures** | Screening  Day -7 to -1 | Enrollment/Baseline  Visit 1, Day 1 | Study Visit 2  Day 7 +/-1 day | Study Visit 3  Day 14 +/- 1 day | Study Visit 4  Day 21 +/-1 day | Study Visit 5  Day 28 +/-1 day | Study Visit 6  Day 35 +/-1 day | Study Visit 7  Day 42 +/-1 day | Study Visit 8  Day 49 +/-1 day | Study Visit 9  Day 56 +/-1 day | Study Visit 10  Day 63 +/-1 day | Study Visit 11  Day 70 +/- 1 day | Study Visit 12  Day 77 +/-1day | Final Study Visit 13 Day 84 +/-5 days |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Administer study intervention |  | X |  |  | X |  |  | X |  |  | X |  |  |  |
| Concomitant medication review | X | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | |  |
| Physical exam | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Vital signs | X | X |  |  | X |  |  | X |  |  | X |  |  | X |
| Height | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Performance status | X | X |  | X |  | X |  | X |  | X |  | X |  | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| serum chemistry a | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test b | X |  |  |  | X |  |  | X |  |  | X |  |  |  |
| EKG (as indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse Event review and evaluation | X | X---------------------------------------------------------------------------------------------X | | | | | | | | | | | | X |
| Radiologic/Imaging assessment | X |  |  |  | X |  |  |  | X |  |  |  |  | X |
| Other assessments (e.g., immunology assays, pharmacokineticc) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete Case Report Forms (CRFs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.  b: Serum pregnancy test (women of childbearing potential) prior to administration of the study intervention.  c: Samples taken pre-dose and at 15, 30 45 min, 2, 4, 8 hour post-dose | | | | | | | | | | | | | | |

<Insert table>

# INTRODUCTION

*The following subsections should include relevant background information and rationale for the clinical trial. This should be a brief overview (e.g., approximately 1-7 pages). Referring to the Investigator’s Brochure (IB), product monograph or device manual for more detail is also appropriate.*

## Study Rationale

*State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial*

<Insert text>

## Background

*This section should include:*

* *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance*
* *A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies*
* *Discussion of any pediatric data, included case report, or meta-analysis pediatric studies*
* *Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in* ***Section 11, References****)*
* *Applicable clinical, epidemiological, or public health background or context of the clinical trial*
* *Importance of the clinical trial and any relevant treatment issues or controversies*

<Insert text>

## Risk/Benefit Assessment

*Summarize the known risks and benefits to participants; this should be a high level summary (not a list of every possible Adverse Event) of information available in the package insert, device labelling, product monograph or Investigator’s Brochure (IB) and from relevant published literature and your own data.*

*Describe any immediate or long-range physical, psychological, social, legal, or any other potential risks or benefits to individual participants or, for benefits only, to society in general, as a result of participating in the study*

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

*Include an assessment as to why the value of the information to be gained outweighs the risks of participation in the study.*

# OBJECTIVES AND ENDPOINTS

*Provide a description of the study objectives and endpoints, as well as a justification for selecting the particular endpoints, in the table format included below*.  *Each endpoint and data point must link to achieving an objective. The objectives and endpoint must connect with the study rational and background for the trial and be consistent with the Objectives and Endpoints outlined in* ***Section 1.1, Synopsis****.*

An **objective** is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as 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 behaviour).

*A* ***study endpoint*** *is a specific measurement or observation to assess the effect of the study variable (study intervention). Give succinct, but precise definitions of the study endpoints used to address the study’s primary objective and secondary objectives (e.g., specific laboratory tests that define safety or efficacy, clinical assessments of disease status, assessments of psychological characteristics, patient reported outcomes, behaviours or health outcomes). Include the study visits or time points at which data will be recorded or samples will be obtained.*

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
| --- | --- | --- |
| Primary |  |  |
| The primary objective is the main scientific question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).  [Phase 1:  To estimate the maximum tolerated dose (MTD) or optimum biological dose and/or recommended Phase 2 dose of \_\_\_\_\_\_\_\_\_\_\_\_\_ administered as a\_\_\_\_\_\_\_\_\_\_\_\_\_, every X -days to pediatric patients with xxxxx.]  [To define and describe the toxicities of \_\_\_\_\_\_\_\_\_\_ administered on this schedule.]  [To characterize the pharmacokinetics of \_\_\_\_\_\_\_\_\_\_\_ in pediatric patients with xxxxxxx.]  Phase 2:  [To define activity of \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_in pediatric patients with <insert disease types being studied>.] | The primary endpoint(s) should be clearly specified and its importance and role in the analysis and interpretation of study results should be defined. The primary endpoint(s) is the basis for concluding that the study met its objective (e.g., “the study wins”).  Generally, there should be just one primary endpoint that will provide a clinically relevant, valid, and reliable measure of the primary objective. Additional primary endpoints may require an adjustment to the sample size calculations and p-value threshold.  In a trial designed to establish efficacy, a primary endpoint should measure a clinically meaningful therapeutic effect or should have demonstrated ability to predict clinical benefit. | Briefly explain why the endpoint(s) were chosen; reflect on the study rationale and background. |
| Secondary |  |  |
| The secondary objective(s) are goals that will provide further information on the use of the intervention. | Secondary endpoints should be clearly specified and may include, for example, endpoints related to efficacy, safety, or both. Secondary endpoints are those that may provide supportive information about the study intervention’s effect on the primary endpoint or demonstrate additional effects on the disease or condition. It is recommended that the list of secondary endpoints be short, because the chance of demonstrating an effect on any secondary endpoint becomes increasingly small as the number of endpoints increases. | Briefly explain why the endpoint(s) were chosen; reflect on the study rationale and background. |
| Exploratory |  |  |
| *Exploratory objective(s) serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research.* | *Exploratory endpoints should be specified.* *Exploratory endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore new hypotheses.* | *Briefly explain why the endpoint(s) were chosen; reflect on the study rationale and background.* |

# STUDY DESIGN

## Overall Design

*The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should be consistent with* ***Section 1.1,******Protocol Synopsis and Section 1.2, Protocol Schema*** *and include:*

* *A statement of the hypothesis*
* *Phase of the trial; for Phase 1 trials, contact Clinical Research Services at* [aSK.CRS@sickkids.ca](mailto:aSK.CRS@sickkids.ca) *for additional resources.*
* *A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design; Refer to the* [glossary](http://my.sickkids.ca/research/clinical-research-services/Pages/Glossary.aspx) *for definitions)*
* *A description of methods to be used to minimize bias*
* *The number of study groups/arms and study intervention duration*
* *Indicate if single site or multi-site*
* *Name of study intervention(s); if one or more of the interventions is standard of care, ensure this is clearly stated*
* *Name of sub-studies, if any, included in this protocol*

<Insert text>

## Scientific Rationale for Study Design

*Describe the rationale for the type and selection of control (e.g., placebo, active drug, dose-response, historical) and study design (e.g., non-inferiority as opposed to superiority). Discuss known or potential problems associated with the control group chosen in light of the specific disease and intervention(s) being studied. If specific populations are excluded (e.g., elderly or pediatric populations, women or minorities), provide a clear and compelling rationale and justification, to establish that inclusion is inappropriate with respect to the health of the participants or the purpose of the research.*

<Insert text>

## End of Study Definition

*A clinical trial is considered completed when participants are no longer being examined or the last participant’s last study visit has occurred.*

[A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in **Section 1.3, Schedule of Activities (SoA)**. The duration of participation for each individual participant who completes all study visits will be *<*X> months.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. It is estimated that it will take <XX> months from when the study opens to enrollment until the end of the study.]

# STUDY POPULATION

The following subsections should include a description of the study population and participant recruitment. The study population should be appropriate for the clinical trial phase and the development stage of the study intervention.

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

* The eligibility criteria should provide a definition of participant characteristics required for study entry/enrollment.
* Informed Consent must be obtained prior to screening procedures required to determine eligibility.
* The risks of the study intervention should be considered in the development of the inclusion/exclusion criteria so that risks are minimized.
* 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 old as an exclusion criterion).
* Identify specific laboratory tests or clinical characteristics that will be used as criteria for enrollment or exclusion.
* Include reproductive status (e.g., pregnancy, lactation, reproductive potential) as an eligibility criterion, if applicable for the study population.
* If you have more than one study population, please define the common inclusion and exclusion criteria followed by the specific inclusion and exclusion criteria for each subpopulation.

## Inclusion Criteria

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.

Some criteria to consider for inclusion are: provision of appropriate consent and assent, willingness and ability to participate in study procedures, age range, health status, specific clinical diagnosis or symptoms, background medical treatment, laboratory ranges, and use of appropriate contraception. 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. Ability to take oral medication and be willing to adhere to the <study intervention> regimen
6. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration
7. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner during study participation and for an additional <specify duration> weeks after the end of <study intervention> administration]

<Insert text>

## Exclusion Criteria

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.

Some criteria to consider for exclusion are: pre-existing conditions or concurrent diagnoses, concomitant use of other medication(s) or devices, known allergies, 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.

*Include a statement regarding equitable selection or justification for excluding a specific population.*

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

1. Current use of < specify disallowed concomitant medications*>*
2. Presence of <specific devices (e.g., cardiac pacemaker)>
3. Pregnancy or lactation
4. Known allergic reactions to components of the <study intervention>, <specify components/allergens>
5. Febrile illness within <specify time frame*>*
6. Treatment with another investigational drug or other intervention within *<*specify time frame*>*
7. Current smoker or tobacco use within *<*specify timeframe*>*
8. Current cannabis user or use within <specify timeframe>
9. < Specify any condition(s) or diagnosis, both physical or psychological, or physical exam finding that precludes participation>
10. Any condition or diagnosis, that could in the opinion of the Principal Investigator or delegate interfere with the participant’s ability to comply with study instructions, might confound the interpretation of the study results, or put the participant at risk]

<Insert text>

## Lifestyle

*Restrictions should only be included if their use has an impact or could potentially have an impact on the study results;* ***if not applicable, delete this section****.*

*Describe any restrictions during any parts of the study pertaining to lifestyle and/or diet (e.g., food and drink restrictions, timing of meals relative to dosing, intake of caffeine, alcohol, or tobacco, or limits on activity), and considerations for interactions with others who are immunocompromised; ensure these restrictions are details in the Informed Consent Form. Describe what action will be taken if restrictions are not followed (e.g., early withdrawal).*

[During this study, participants are asked to:

* Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, [pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices] from [X days] before the start of <study intervention> until after the final dose.
* Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for [x hours] before the start of each dosing session until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
* Abstain from alcohol for [x hours] before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample.
* Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
* Abstain from cannabis for [x hours] before the start of each dosing session until after collection of the final PK and/or pharmacodynamic sample.
* Abstain from strenuous exercise for [x hours] before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
* Minimize interactions with others who may be immunocompromised.

Participants who do not meet these criteria prior to the start of the <study intervention> will be considered a screen failure, but may rescheduled if they meet the criteria to be re-screened. Participants who do not meet these criteria following the start of the <study intervention> will be assessed by the Principal Investigator or delegate and may be withdrawn from the study.]

<Insert text>

## Screen Failures

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures. Indicate how screen failures will be handled in the trial, including conditions and criteria upon which re-screening is acceptable (e.g. how often?, how many times?), when applicable.

[Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a <specify modifiable factor> may be rescreened after <x> <weeks or months> to a maximum of <x> times. Rescreened participants should be assigned the same participant number as for the initial screening.]

<Insert text>

## Strategies for Recruitment and Retention

Identify general strategies for participant recruitment and retention. This section may refer to a separate detailed site specific recruitment and retention plan in a site-specific standard operating procedure (SOP). Consider inclusion of the information below in this section.

* *Target study sample size by gender, race and ethnicity, and age; identify anticipated number to be screened including women and minorities in order to reach the target enrollment* (should be consistent with information contained in **Section 9.2, Sample Size Determination**)
* Anticipated accrual rate
* Anticipated number of sites and participants to be enrolled from Canada and outside of Canada; Do not list all of the sites or countries as this requires an amendment if there are changes
* Source of participants *(e.g., inpatient hospital setting, outpatient clinics, school board, general public, or use of databases or referrals)*
* If the study requires long-term participation, describe procedures that will be used to enhance participant retention (e.g., multiple methods for contacting participants, visit reminders, incentives for visit attendance)

<Insert text>

# STUDY INTERVENTION

*The following subsections should describe the study intervention that is being tested for safety and effectiveness in the clinical trial, and any control product being used in the trial. Using the NIH definition, an "intervention" is a manipulation of the participant’s environment for the purpose of modifying one or more health-related biomedical or behavioural processes and/or endpoints. This section of the protocol should be used to describe all types of interventions meeting this definition, for example, drugs/small molecules/compounds; biologics; natural health products; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behaviour (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.*

*Submission to Health Canada is likely required when the study intervention is a drug (including a biologic or natural health product), imaging intervention, or device that is intended for administration to humans or use in humans, and that has not yet been approved by Health Canada. This also includes a product with a marketing authorization when used in a way that is different from the approved form (route of administration or dose) or when used for an unapproved indication or population (e.g., pediatrics) even when this use reflects standard of care.*

*Contact Clinical Research Services for a regulatory consultation on the need for Health Canada submission (*[aSK.CRS@sickkids.ca](mailto:aSK.CRS@sickkids.ca)*).*

***The subheadings should be updated as appropriate to reflect the type of intervention being tested.***

*A****ll sections may not be relevant for the trial; if not relevant, delete the subsection.***

## Study Intervention(s) Administration

### Study Intervention Description

*Describe the study intervention(s) and placebo or control product. Product information can usually be obtained from the:*

* *IB for an investigational drug, biological or natural health product*
* *Package insert/product monograph for a licensed or approved drug, biological or natural health product, or device manual for a licensed device*
* *Proposed labeling and/or material safety data sheet (MSDS) for an investigational device*
* *Final labeling for a marketed device*

*If an intervention is a standard of care arm, include justification supporting use as standard of care referring to the product monograph or supporting literature.*

*In addition:*

* *Indicate if the study intervention is commercially available and is being used in accordance with approved labeling. For a device, note if any modifications will be performed for the study.*
* *If conducting a study with a device, the following information should be included:*
  + *Device size(s)*
  + *Device model(s)*
  + *Description of each component*
  + *Device settings and programming (if applicable)*
  + *Duration of implant or exposure (if applicable)*
  + *Frequency of exposure (if applicable)*
  + *If a device has not been approved or cleared for the indications the protocol is designed to investigate, then a summary/report of test validation studies should accompany this protocol*

<Insert text>

### Dosing and Administration

*Describe the procedures for selecting the dose of study intervention and placebo or control product. For drug, biological and natural health products, include:*

* *Dose, including a justification for the planned starting and maximum dosage, and dosing regimen*
* *Timing of dosing (e.g., time of day, frequency) and relation of dosing to meals*
* *Route of administration (e.g., oral, nasal, intramuscular) including justification for selected route*
* *Duration, the length of time study participants will be administered the study intervention*
* *Any specific instructions to study participants about when or how to prepare and take the dose(s), including how delayed or missed doses should be handled*
* *Any specific instructions or safety precautions for administration of the study intervention, such as, the maximum time once thawed/mixed, if appropriate, before administration*

*While much of the above section is specific to drugs, similar considerations apply to certain devices and other types of interventions. For example, some devices have adjustable settings including those related to energy delivery to participants. Other devices must be sized correctly for individual participants. Similar to the discussion above for dosage of drugs, such considerations should be described for all types of study interventions, as applicable. Modify the subheading as needed.*

<Insert text>

### Dose Escalation and Modifications

*Describe the dose escalation scheme and dose regimen (using exact dose, rather than percentages). State any minimum period or other requirements (e.g., Data Safety Monitoring Board (DSMB) or medical monitor approval) required before a participant’s dose might be raised to the next higher dose or dose range. If applicable, the protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy). Address dose modifications for specific abnormal laboratory values of concern or other Adverse Events (AEs) that are known to be associated with the planned study intervention. The protocol must state explicitly the dose-limiting effects that are anticipated. Provide criteria that will be used to determine dose escalations. If a participant is responding positively to the intervention, the protocol should specify whether study intervention administration would progress to still higher doses. If appropriate, provide a dose de-escalation schema with intervention modifications. Do not restate reasons for withdrawal of participants.*

*While much of the above section is specific to drugs, similar considerations apply to other types of interventions; modify as appropriate.*

<Insert text>

## Preparation/Handling/Storage/Accountability

*For drug, biological or natural health product interventions contact Research Support Pharmacy for a consultation at* [pharmacy.research@sickkids.ca](mailto:pharmacy.research@sickkids.ca)*.*

### Acquisition and Accountability

*State how the study intervention and placebo or control product will be obtained. Describe plans about how and by whom (use organization name and/or titles, not individuals’ names) the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.*

<Insert text>

### Formulation, Appearance, Packaging, and Labeling

*Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device manual or labeling. This section should include the name of the manufacturer of the study intervention and control product for non-marketed products or when the manufacturer will not change throughout the duration of the study. Where the study intervention or control product are marketed drugs acquired through hospital supply, do not list the manufacturer in the event that the supplier may change.*

<Insert text>

### Product Storage and Stability

*Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and placebo or control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).*

<Insert text>

## Measures to Minimize Bias: Randomization and Blinding

*This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated). In addition, details regarding the implementation of procedures to minimize bias should be included in this section. DO NOT include details that might compromise these strategies. Design techniques to avoid bias can be found in the ICH Guidance for Industry E9 Statistical Principles for Clinical Trials.*

*Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed; including:*

* *timing and procedures for planned and unplanned breaking of randomization codes,*
* *efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible,*
* *measures to prevent unblinding by laboratory measurements, if used,*
* *where some Investigators to remain unblinded (e.g., to allow them to adjust medication), describe the means of shielding other Investigators,*
* *a statement regarding when unblinding may occur and who may unblind, and the criteria for breaking the study blind or participant code,*
* *the circumstances in which the blind would be broken for an individual or for all participants (e.g., for Serious Adverse Events (SAEs)),*
* *plans to manage and report inadvertent unblinding,*
* *whom the intentional and unintentional breaking of the blind should be reported.*

*Sometimes blinding is attempted but is known to be imperfect because of obvious effects related to study intervention or control product in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, and changes in laboratory data). Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by study staff shielded from information that might reveal study group assignment).*

*If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained (e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias). If blinding is considered desirable but not feasible, the reasons and implications should be discussed.*

<Insert text>

## Study Intervention Compliance

*Define how adherence to the protocol (e.g., administration of study intervention, use of device) will be assessed, and verified, if applicable (e.g., plasma assays, electronic monitoring devices, daily diaries). Include a discussion of what documents are mandatory to complete (e.g., participant drug log) and what source documents/records will be used to calculate study intervention compliance.*

<Insert text>

## Concomitant Therapy

Include content in this section if applicable, otherwise delete the section.

*Describe permitted, restricted (allowed but must be used with precautions to ensure safety) and prohibited concomitant medications, supplements, complementary and alternative therapies, treatments, and/or procedures. This section should include discussion of supportive care if applicable but should be in general terms and not prescribe details or specific drugs and doses. Restricted and prohibited medications should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed.*

*Include details about what will be recorded and when the information will be collected (e.g., screening, all study visits; this must match the SoA) and when collection of this information will end. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints) and how the independent effects of concomitant and study interventions could be ascertained.*

[Supportive care will be administered as needed in accordance with SickKids standard clinical practices. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.]

[Narcotics/opioids will be the only concomitant medications collected for this trial. All narcotics/opioids given within 6 hours of study medication initiation up to 6 hours post extubation will be documented in the CRF, except in the case of a Serious Adverse Event (SAE), where all concomitant medications for the SAE will be captured.]

[Over the counter and prescription medications are restricted from 14 days before baseline until 30 days after the final dose of the study intervention. Participants will be instructed to contact the study team prior to initiating any new medications if possible and to inform the study team of any medications they have taken at each study visit.]

[Use of the following medications is prohibited while participants are on the study intervention: 1) XXXXXXX, 2) XXXXXXXX. The need for ongoing use of these medications would be exclusionary at study entry, but would be recorded as a concomitant medication if medically indicated and prescribed during the course of the study.]

<Insert text>

# DISCONTINUATION and WITHDRAWAL

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. This section should state which Adverse Events would result in discontinuation of study intervention or participant discontinuation/withdrawal. In addition, participants may discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable).

## Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any safety monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of Adverse Events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of, or rechallenging with, study intervention. Discuss the role of the DSMB and/or medical monitor in making decisions to discontinue study intervention, if applicable.

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture Adverse Events (AE) and Serious Adverse Events (SAE).

[Discontinuation from <study intervention> does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the PI or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an Adverse Event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

* <Describe the procedures and data to be collected, as well as any follow-up evaluations>]

<Insert text>

## Participant Discontinuation/Withdrawal from the Study

Provide a list of reasons participation may be discontinued. It may be appropriate to provide distinct discontinuation criteria for participants and groups/arms. 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 or discontinue the study intervention at any time.

In studies of gene therapy or implantable devices, a discussion should be included of any pertinent information that will be provided to withdrawn or discontinued participants (e.g., inability to remove gene therapy and impact for future gene therapy, whether and how the device can be removed, how to replace batteries, how to obtain replacement parts, who to contact). In addition, it is important to capture the reason for withdrawal or discontinuation, as this may impact inclusion of participant data in the analysis of results (see **Section 9, Statistical Considerations**).

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 9, Statistical Considerations.**

[Participants are free to withdraw from participation in the study at any time upon request.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

* Withdrawal of informed consent (participant or parent/guardian withdraw for any reason)
* 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
* Significant study intervention non-compliance
* Disease progression which requires discontinuation of the study intervention
* Requirement of prohibited concomitant medication(s) that requires discontinuation of the study intervention
* If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
* Pregnancy
* Participant unable to receive <study intervention> for [x] days/weeks.]

The reason for participant discontinuation or withdrawal from the study will be recorded in the study file <include name of document or CRF, if known>. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, <will> *or* <will not> be replaced. The data from participants who are withdrawn or discontinued from the study will be used in the analysis unless the participant requests otherwise.]

<Insert text>

## Lost to Follow-Up

The protocol should describe the nature and duration of study follow-up. Validity of the study is a potential issue when participants are lost to follow-up, as information that is important to the endpoint evaluation is then lost. Participants are considered lost to follow-up when they stop reporting to scheduled study visits and cannot be reached to complete all protocol-required study procedures. Describe the plans to minimize lost to follow-up and missing data.

[A participant will be considered lost to follow-up if they fail to return for <specify number of visits> scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

* The site will attempt to contact the participant and reschedule the missed visit <specify time frame> and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
* Before a participant is deemed lost to follow-up, the Principal Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record or study file.
* Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

<Insert text>

# STUDY ASSESSMENTS AND PROCEDURES

*Clearly differentiate assessments and procedures that are done as part of clinical care where the study will collect the data from the medical record and those assessments and procedures that are done exclusively for the study; this has an impact on the study budget and billing.*

## Assessments

*List and describe all study procedures and evaluations to be done as part of the study to support the determination of efficacy and safety or that are done for other study purposes (e.g., screening, eligibility, enrollment). The specific timing of procedures/evaluations to be done at each study visit are captured in* ***Section 1.3, Schedule of Activities (SoA)*** *and the time points of these procedures* ***do not*** *need to be included here. Note that the protocol should provide a high-level discussion of all procedures and detailed information can be further provided in a Manual of Procedures (MOP), SOP or Laboratory Manual, if needed.*

*Discuss the sequence of events that should occur during the screening process and any decision points regarding participant eligibility. Include the time frame prior to enrollment within which screening procedures/ evaluations must be performed (e.g., within 28 days prior to enrollment). If pre-screening is required to identify participants for this study, describe what data will be reviewed and how it will be handled. In addition, discuss any special conditions that must be achieved during the enrollment and/or initial administration of study intervention.*

*If an individual’s medical chart or results of diagnostic tests performed as part of an individual’s regular medical care are going to be used for screening or as a part of collection of trial data, Personal Health Information Protection Act (PHIPA) and local institutional requirements should be followed, as applicable. If this is the case, this section should note which information is to be obtained through review of existing data.*

*Include the procedures for administering the study intervention and follow-up procedures after administration (e.g., assessment of vital signs), as well as any specifics about subsequent follow-up visits, and unscheduled visits. Also, note if a specifically qualified person (e.g., physician, psychologist) should be performing any of the assessments. Fully explain any definitions used to characterize outcomes (e.g., criteria for determining occurrence of acute myocardial infarction, characterization of a stroke as thrombotic or hemorrhagic, distinction between transient ischemic attack and stroke).*

*As part of the description of the study procedures and evaluations, include:*

* *justification for any sensitive procedures (e.g., provocative testing, deception),*
* *approaches to decrease variability, such as centralized laboratory assessments, where applicable,*
* *where appropriate, that procedures/evaluations will be performed by qualified personnel,*
* *a discussion of the results of any study specific procedures that will be provided to participant (e.g., radiographic or other imaging or laboratory evaluations).*

*This section may include a list and description of the following procedures/evaluations, as applicable:*

* ***Physical examination*** *(e.g., height and weight, organ systems, motor or vision assessment, or other functional abilities). If appropriate, discuss what constitutes a targeted physical examination.*
* ***Vital signs*** *(e.g., temperature, pulse, respirations, blood pressure). Carefully consider which vital signs (if any) should be measured to ensure that only essential data are collected. Include any specific instructions with respect to the collection and interpretation of vital signs.*
* ***Electrocardiograms (EKGs)*** *specify if the EKG is for screening purposes only. Include any specific instructions for the collection and interpretation of the EKG (e.g., time points relative to dosing with study intervention or other evaluations). If EKGs will be analyzed at a central laboratory, instructions for the collection (e.g., equipment), transmission and archiving of the EKG data should be summarized in this protocol, and further outlined in the MOP. If the EKG will be read locally, indicate how these will be handled and in what format (e.g., digital or paper), as well as instructions with respect to local review.*
* ***Radiographic or other imaging assessments*** *State the specific imaging required and, as appropriate, provide description of what is needed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion and equipment specifications may be described in the study’s MOP or a separate SOP.*
* ***Biological specimen collection and laboratory evaluations*** *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-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. If the sample will be analyzed in a research laboratory or any laboratory that is not accredited, ensure the SickKids institutional* [guideline on best practices for research laboratory testing](http://my.sickkids.ca/research/clinical-research-services/Pages/Translational-Research.aspx) *is followed. In addition, discussion should include whether any laboratory tests (e.g., diagnostics) that will be used are being developed concurrently or are commercially available. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP or a separate SOP or Laboratory Manual.*
* ***Special assays or procedures required*** *(e.g., immunology assays, pharmacokinetic studies, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. If more than one laboratory will be used, specify which assays will be done by each laboratory. If the sample will be anaylsed in a research laboratory, ensure the SickKids institutional* [guideline on best practices for research laboratory testing](http://my.sickkids.ca/research/clinical-research-services/Pages/Translational-Research.aspx) *is followed. Special instructions for the preparation, handling, storage, and shipment of specimens should be briefly explained in this section with detailed discussion in the study’s MOP or a separate SOP or Laboratory Manual.*
* ***Counseling procedures, including any dietary or activity considerations*** *that need to be adhered to during study participation.*
* ***Assessment of study intervention adherence***
* ***Administration of questionnaires or other instruments*** *for patient-reported outcomes, such as a daily diary.*
* ***Procedures that will be completed during the study as part of regular standard of clinical care***

<Insert text>

## Adverse Events and Serious Adverse Events

*The following subsections should highlight safety assessments and aspects of the study which are proposed to ensure the safety of trial participants. Consider the risks of the study intervention and other study procedures and the characteristics of the study population (e.g., vulnerable populations such as children). Review and reference the applicable sources of information, such as the IB, product monograph, package insert, device manual or labeling, literature and other sources that describe the study intervention. This section should be tailored for specific study characteristics, such as:*

* *Use of an investigational new drug or investigational device*
* *Washout from current medication regimen*
* *Use of placebo in a population with a diagnosed disease*
* *Selection of an appropriate toxicity grading scale*
* *Risks to individuals other than research participants (e.g., household or intimate contacts or communities, study clinicians, pharmacists or interventionists, etc.)*
* *Reporting of certain events (e.g., suspected child abuse) is mandatory because of the study population*
* *The study is conducted at multiple sites, and will require centralized safety oversight*

*Refer to the current version of SickKids guideline: ‘Reporting of Unanticipated Problems (UP) including Serious Adverse Events and Protocol Deviations by Investigators to the SickKids Research Ethics Board.’*

### Definition of Adverse Events (AE)

*Provide the definition of an AE being used for the clinical trial.*

[An Adverse Event (AE) is any untoward medical occurrence associated with the use of an intervention in a study participant, which does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the intervention, whether or not considered related to the investigational intervention.

Stable chronic conditions which are present prior to entry in the study and do not worsen are not considered AE. These pre-existing conditions will be documented in the participant’s medical history.]

<insert text>

### Definition of Serious Adverse Events (SAE)

*Provide the definition of an SAE being used for the clinical trial.*

[AE are classified as serious or non-serious.  A Serious Adverse Event is any AE that is:

* fatal
* life-threatening
* requires or prolongs inpatient hospital stay
* results in persistent or significant disability or incapacity
* a congenital anomaly or birth defect
* an important medical event

The term “life-threatening” in the definition of “serious” refers to an AE in which the participant was at risk of death at the time of the event. It does not refer to an AE that hypothetically might have caused death if it were more severe.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.  They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above.  Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse]

*Device example text:*

[Serious Adverse Events will be documented for any incident that:

1. is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its directions for use; and
2. has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. “Serious deterioration in the state of health” means: a life-threatening disease, disorder or abnormal physical state; the permanent impairment of a body function or permanent damage to a body structure; or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.]

<Insert text>

### Classification of an Adverse Event

*The following subsections will include a discussion of how AEs will be classified.*

#### Severity of Event

*All AEs will be assessed by the study clinician using a protocol defined grading system. Describe the method of grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs. For Phase 1 and specific disciplines, such as Oncology, please contact Clinical Research Services at* [aSK.CRS@sickkids.ca](mailto:aSK.CRS@sickkids.ca) *to resources for toxicity grading.*

[The severity of an AE is assessed by a qualified physician who is part of the study team, who should use the following definitions when assessing the intensity of an AE:

* **Mild** – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
* **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
* **Severe** – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.]

<Insert text>

#### Relationship to Study INTERVENTION

*All AEs will have their relationship to study intervention or study participation assessed with a level of specificity appropriate to the study design; describe the method of determining the relationship of an AE to a study intervention.*

[All Adverse Events (AEs) must have their relationship to the study intervention assessed by a qualified physician who is part of the study team based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

* **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible.
* **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
* **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events).
* **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
* **Unrelated** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.]

<Insert text>

#### Expectedness

*Expected adverse reactions are AEs that are known to occur for the study intervention being studied. Expectedness is assessed based on the awareness of AEs previously observed (listed in product monograph, IB, package inserts, or device manual), not on the basis of what might be anticipated from the properties of the study intervention.*

[A qualified physician who is part of the study team 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.]

<Insert text>

### 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. Include duration following study completion where AEs and SAEs reported will be recorded and assessed as part of the study; consider the duration of the study and washout period for the study intervention when determining the duration of follow-up.*

[All Adverse Events (AEs) or Serious Adverse Events (SAEs) with start dates occurring any time after receiving the study intervention until <7> days (for non-serious AEs) or <30> days (for SAEs) after the last day of study intervention will be documented. The occurrence of an AE or SAE may be detected during study tests (e.g. clinically significant laboratory results), spontaneously reported by the participant/parent or guardian to the research team, elicited by appropriate questioning during clinical evaluations or gathered during telephone follow-up calls. At each study visit, the participant will be asked about any change in their health since the last visit and for any changes to AE and SAEs that were ongoing at the last visit or telephone contact.

All AEs and SAEs occurring while on study must be documented regardless of relationship. Information to be collected includes event description, date and time (if possible) of onset, date and time (if possible) of resolution/stabilization of the event, outcome, and the assessment of seriousness, expectedness, relationship to study intervention and severity by a delegated qualified physician.

Any baseline condition recorded in the medical history that deteriorates at any time during the study, will be recorded as an AE or SAE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

Events will be followed for outcome information until resolution or in the opinion of the PI or qualified physician delegate, the participant is stable and does not require further follow-up, or the participant is deemed lost to follow-up.]

<Insert text>

### Adverse Event Reporting

*Describe responsibilities of Investigators and SickKids as the Sponsor and procedures for reporting of AEs, including timeframes. This should include any reporting requirements to the medical monitor, DSMB or other independent oversight body (e.g., safety monitoring committee, independent safety monitor, etc.), REB, regulatory agencies, etc.*

*In addition, list any disease-related events (DREs) common in the study population (i.e., expected), which will not be reported per the standard process for reporting, as applicable. Describe how these events will be recorded and monitored.*

[AE will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children’s Adverse Event Reporting Requirements.]

For multi-center trials:

[AE will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children’s Adverse Event Reporting requirements and as per local institutional and regulatory requirements at each site.]

<Insert text>

### Serious Adverse Event Reporting

*Describe responsibilities of Investigators and SickKids as the Sponsor and procedures for reporting of SAEs. This should include any reporting requirements to the medical monitor, DSMB or other independent oversight body (e.g., safety monitoring committee, independent safety monitor, etc.), REB, regulatory agencies, etc.. Three examples are provided below for Health Canada regulated trials (drug and biologic, device and natural health product), modify this section in accordance with your trial and delete example language as appropriate.*

***Example 1, applicable for a drug or biologic protocol, modify multi-center language as necessary for single site studies:***

[All Serious Adverse Events (SAE) must be reported to Dr. <PI name> within 24 hours of becoming aware of the SAE. The initial report must be <emailed/faxed/other> to <insert email addresses and/or fax number> and should contain as much information as available, at a minimum, the report must contain:

* Name of Site and Principal Investigator,
* Participant Identification Code,
* Adverse Event Term,
* Study Drug Dose and Start/Stop Dates

On the next working day email completed trial-specific Serious Adverse Event form or Council for International Organizations of Medical Sciences (CIOMS) form.

**Only adverse drug reactions that are *both* serious and unexpected are subject to expedited reporting to Health Canada.** Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

*For multi-center trials, include* <AE will be reported in accordance with site REB and regulatory authorities in accordance with local institutional and regulatory requirements.>

During a clinical trial the Sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction (SUADR) that has occurred inside or outside Canada:

1. where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
2. where it is fatal or life-threatening, immediately where possible and, within 7 days after becoming aware of the information; and
3. within 8 days after having informed Health Canada of the SUADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings. Final reports of fatal or life-threatening reactions must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

Each SUADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada / ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

In situations when causality assessment and determination of expectedness is not straightforward, the report should be submitted in the expedited manner and the relevant issues addressed in a cover letter.

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgment should be applied to each situation. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations; including:

1. for an "expected" serious Adverse Drug Reaction (ADR), an increase in the rate of occurrence which is judged clinically important;
2. a significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease; and
3. a major safety finding from a newly completed animal study.

Adverse events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children’s Adverse Event Reporting Requirements.

Dr. <PI name> will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial as described above. Investigators must notify their Research Ethics Boards (REBs) according to institutional requirements and file the report and acknowledgement from the REB (e.g. letter from the REB acknowledging receipt, stamp from the REB, signed and dated by REB chair or delegate, acknowledging receipt) with their Investigator Site File.

Expedited Serious Adverse Events occurring within a center should also be reported to local REBs according to institutional requirements.

The Data Safety Monitoring Board (DSMB) will be notified by <email/ fax/other> to <insert email addresses and/or fax number> of all unexpected Adverse Events within 7 days and serious, unexpected Adverse Events within 48 hours.]

***Example 2, applicable for device protocol:***

[The Health Canada Medical Devices Regulations require adverse incidents or problems experienced with medical devices that meet the criteria of an SAE within Canada to be reported to the Health Product and Food Branch Inspectorate in the following manner:

* Where it is neither fatal nor life threatening, within 30 days after becoming aware of the information;
* Where the device has caused a fatal outcome or deterioration in the health of a research participant, user, or another person, reporting should be immediate where possible, and, in any event within 10 days after becoming aware of the information.

Please refer to the regulations for reporting adverse incidents or problems with devices being used outside of Canada.

Adverse Events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children’s Adverse Event Reporting Requirements, as well as any applicable local institutional or regulatory regulations.]

***Example 3, applicable for Natural Health Product protocol:***

[Serious, unexpected, AEs/ADRs which occur within or outside of Canada should be reported according to the following criteria:

* Where it is neither fatal nor life threatening, within 15 days after becoming aware of the information,
* Where it is fatal or life threatening, immediately where possible, and, in any event within 7 days after becoming aware of the information,
* Within 8 days after having informed Health Canada, submit as complete a report as possible including an assessment of the importance and implication of any findings.

Adverse events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children’s Adverse Event Reporting Requirements, as well as any applicable local institutional or regulatory requirements.]

<Insert text>

### Reporting Events to Participants

*Describe how participants will be informed about AEs and SAEs, and study-related results on an individual or aggregate level. In addition, describe plans for detecting and managing secondary/incidental findings associated with study procedures. Ensure that studies with research genetic testing follows the SickKids* [Guidelines for Research Genetic testing](http://my.sickkids.ca/research/clinical-research-services/Documents/TRWG/Guidelines_Genetic_Testing%20August%2024%202018v2.pdf)*.*

[Participants and/or their parent/legal guardian will be informed in a timely manner of any new information, including safety information, that is relevant to that participant’s willingness to continue participation. The communication of this information will be documented through a revised REB approved Informed Consent Form, where possible, based on the timeliness of the information.]

*Example language for general incidental findings:*

[In the event that a study procedure detects a new clinically important secondary finding/incidental finding, the qualified physician will notify the Most Responsible Physician (MRP) physician at SickKids (if the participant is being treated at SickKids) or request the participant’s family doctor’s name and contact information in order to arrange medical follow-up to interpret the significance of the findings.]

*Example language for incidental findings in genetic studies (refer to* [Enabling Clinical Translation (ENACT)](http://my.sickkids.ca/research/clinical-research-services/Pages/Translational-Research.aspx) *for more information; ensure information is consistent with the* [genetic consent language](http://my.sickkids.ca/research/clinical-research-services/Pages/FAQ.aspx)*):*

[In the event of discovering a medically actionable incidental finding or if any new clinically important information about the participant’s health is obtained as a result of participation in the study and where a second sample is already available, the test result will be validated clinically in an accredited laboratory. Where a second sample is not available for confirmation or where validation of the test has been done, the participant will be informed in consultation with clinical medical genetics. The qualified physician will work with the participant and/or their parent/legal guardian, their family physician and MRP at SickKids (if applicable) to arrange referral to the appropriate specialist as needed.

Decisions on medically actionable incidental findings will be made based on the current version of the American College of Medical Genetics and Genomics (ACMG) list of variants. In the event of medically non-actionable findings based on the ACMG list of variant, the participant and/or their parent/legal guardian will not be informed and the results will not be added to the medical records at SickKids. If the incidental findings reveal information about the participant’s carrier status the participant and/or their parent/legal guardian will be given the opportunity to decide about receiving the carrier status information.]

<Insert text>

### Events of Special Interest

*Describe any other events that merit reporting to the Sponsor, medical monitor, DSMB, REB, and regulatory agencies. For example, in oncology trials, secondary malignancies are often captured.*

*Include any other reportable events not already included in the previous sections, such as cardiovascular and death events, medical device incidents (including malfunctions), laboratory test abnormalities, and study intervention overdose.*

<Insert text>

### Reporting of Pregnancy

*Pregnancy is not an Adverse Event, but some studies will require unique considerations if pregnancy was to occur during the study.*

*State the study’s pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the Sponsor, medical monitor, DSMB, REB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).*

[If a participant becomes pregnant, the study drug will be permanently discontinued and the participant will complete the evaluations/procedures for the early termination visit. The participant will continue to be followed throughout the pregnancy until completion or until pregnancy termination (induced abortion).

Pregnancy will be documented in the study file and any unexpected complications during the pregnancy will be documented as an AE. The outcome of a normal pregnancy will be documented on the Pregnancy Form, however, if the outcome meets the criteria for classification as a SAE, (e.g., ectopic pregnancy, spontaneous abortion, stillbirth, neonatal death or congenital anomaly) this will be documented and reported accordingly.]

<Insert text>

# STATISTICAL CONSIDERATIONS

*The following subsections should describe the statistical tests and analysis plans for the protocol. They should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH Guidance for Industry E9 Statistical Principles for Clinical Trials and the CONSORT statement which describes standards for improving the quality of reporting randomized controlled trials.*

*State whether there will be a formal Statistical Analysis Plan (SAP). A formal SAP should be completed prior to database lock and unblinding of the study data. The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies). If a separate SAP will be developed, subsections below can be summarized.*

*Consult with a statistician when completing Section 9. Support is available through the* [Clinical Trial Unit (CTU)](https://surveys.sickkids.ca/surveys/?s=LJNJXDNMCE) *and* [Clinical Research Services](http://my.sickkids.ca/research/clinical-research-services/Pages/Facilities.aspx)*.*

## Statistical Hypotheses

*State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.*

* Primary Endpoint(s):

<Insert text>

* Secondary Endpoint(s):

<Insert text>

* Exploratory Endpoint(s):

<Insert text>

## Sample Size Determination

*Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants. In particular, specify all of the following:*

* *Outcome measure used for calculations (almost always the primary variable)*
* *Test statistic*
* *Null and alternative hypotheses*
* *Type I error rate (alpha)*
* *Power level (e.g., 80% power)*
* *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
* *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
* *Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc., on study power (see also* ***Sections******9.4.2, Analysis of the Primary Endpoint(s) and 9.4.3, Analysis of the Secondary Endpoint(s)****)*
* *Method for adjusting calculations for planned interim analyses, if any (****Section 9.4.6, Planned Interim Analyses****)*

*Further, present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.*

*Discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term,* ***Section 9.4.9, Exploratory Analyses****).*

<Insert text>

## Populations for Analyses

*Clearly identify and describe the analysis datasets (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:*

* *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
* *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data)*
* *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)*
* *Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)*
* *Other Datasets that may be used for sensitivity analyses*

[The following study populations are defined and will be analyzed as specified below. The population evaluable for safety will be the safety population.

The Intent to Treat (ITT) population: the total population of patients registered in the study.

Safety population: all registered participants who received at least one dose of any study drug.

Efficacy population: all enrolled patients who completed at least one cycle of study drug and had adequate assessment of disease progression.

Any patient who is registered on to this trial but never receives study treatment will be described, including the reason(s) for non-participation.]

<Insert text>

## Statistical Analyses

*The following subsections should include a description of the planned statistical methods. Support is available through the* [Clinical Trial Unit (CTU)](https://surveys.sickkids.ca/surveys/?s=LJNJXDNMCE) *and* [Clinical Research Services](http://my.sickkids.ca/research/clinical-research-services/Pages/Facilities.aspx)*.*

### General Approach

*As a guide, the following should be addressed, as appropriate:*

* *For descriptive statistics, describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range)*
* *For inferential tests, indicate the p-value and confidence intervals for statistical significance (Type I error) and whether one or two-tailed*
* *Indicate whether covariates will be pre-specified in the sections below or later in a SAP*
* *State whether checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests)*

<Insert text>

### Analysis of the Primary Endpoint(s)

*For each primary endpoint:*

* *Define the measurement or observation and describe how it is calculated, if not readily apparent*
* *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
* *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here*
* *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
* *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*
* *Describe the populations for which the analysis will be conducted, as discussed in* ***Section 9.3, Populations for Analyses***
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up*
* *If there is more than one Primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary*

*Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.*

<Insert text>

### Analysis of the Secondary Endpoint(s)

*For each secondary endpoint:*

* *Note if analyses of secondary endpoint(s) are dependent on findings of primary endpoint*
* *Define the measurement or observation and describe how it is calculated, if not readily apparent*
* *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
* *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, ANCOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
* *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (LSMEANS) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, and number-needed-to-treat).*
* *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests).*
* *Describe the populations for which the analysis will be conducted as discussed in* ***Section 9.3, Populations for Analyses.***
* *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up.*
* *If there is more than one secondary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

*Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.*

<Insert text>

### Safety Analyses

*Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in* ***Section 9.4.2, Analysis of the Primary Endpoint(s)*** *should be included here. AE leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within* ***Section 8.1, Assessments****.*

<Insert text>

### Baseline Descriptive Statistics

*Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Discuss planned baseline descriptive statistics, indicate whether inferential statistics will be used.*

[Summary statistics will be used to describe baseline characteristics and other outcomes of interest. Categorical endpoints will be summarized using proportions and frequencies. Continuous endpoints will be summarized using the mean, median, range or standard deviations. Subgroup summarization based on dose level or other criteria may also be conducted.]

<Insert text>

### Planned Interim Analyses

*If an interim analysis is planned, describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing, who performs the statistical analysis, whether they are unblinded and how the blinding will be preserved and who reviews the interim analyses (e.g., DSMB, Medical Monitor, Sponsor). If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.*

*Describe safety findings and statistical rules that would temporarily suspend enrollment and/or study intervention use until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Include whether the proposed rules for halting study enrollment or study intervention/administration of study intervention for safety pertain to the entire study, specific study arms or participant subgroups, or other components of the study.*

*If the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when evaluating results.*

*State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.*

*Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.*

*This section should be consistent with* ***Section 7, Discontinuation and Withdrawal and Section 10.1.5, Safety Oversight.***

[An interim analysis is planned to be performed on the primary endpoint when 50% of patients have been randomized and have completed the follow-up visit. The interim analysis will be performed by an independent statistician, unblinded to the treatment allocation. The statistician will report to the independent Data Safety Monitoring Board (DSMB). The DSMB will have unblinded access to all data and will discuss the results of the interim-analysis and make recommendations to the Sponsor. The Sponsor decides on the continuation of the trial and will report to the REB. A conditional power approach will be used to assess the ability to detect the original hypothesized treatment effect. Should the conditional power be below 0.10 then the continuation of the trial would be considered futile.

The statistical criteria outlined will provide a guideline only for terminating the trial.

Any deviation from the original statistical plan will be described in the final report.]

<Insert text>

### Sub Group Analyses

*Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).*

*Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).*

<Insert text>

### Tabulation of Individual Participant Data

*State whether individual participant data will be listed by measure and time point.*

<Insert text>

### Exploratory Analyses

*Exploratory analyses cannot be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.*

<Insert text>

# SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Regulatory, Ethical, and Study Oversight Considerations

*The following subsections should include a description of the regulatory and ethical considerations, and context for the conduct of the trial. Of note, the guiding ethical principles being followed by this study are included in the* ***Statement of Compliance*** *at the beginning of this protocol and do not need to be repeated here****.***

*For international studies, ensure to indicate that the trial will be conducted in compliance with the applicable local regulatory requirements.*

### Study Discontinuation and Closure

*List possible reasons for termination or temporary suspension of the study (e.g., study closure based on PI decision, Sponsor/funder decision, regulatory or other oversight bodies, DSMB recommendation; review of serious, unexpected, and related AEs; noncompliance; futility). For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the REB, and Sponsor and provide the reason(s) for the termination or temporary suspension.*

*When a study is prematurely terminated, refer to* ***Section******7, Discontinuation and Withdrawal****, for handling of enrolled study participants.*

[This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, Investigator, funding agency, Sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the REB and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

* Determination of unexpected, significant, or unacceptable risk to participants
* Demonstration of efficacy that would warrant discontinuing the trial
* Insufficient compliance to protocol requirements
* Data that are not sufficiently complete and/or evaluable
* Determination that the primary endpoint has been met
* Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, REB, DSMB, and/or regulatory agency.]

<Insert text>

### Confidentiality and Privacy

*This section will describe protections for maintaining confidentiality of participant data, including, but not limited to forms, records and samples and participant privacy.*

*Include procedures for maintaining participant confidentiality, privacy protections, any special data security requirements, and record retention per the Sponsor’s and regulatory authority requirements. Describe who would have access to records, including the Investigator and other study staff, the clinical monitor, funding institutions, representatives of the Sponsor, representatives from the REB, regulatory agencies, and representatives of the pharmaceutical company supplying product to be tested (depending on contractual agreements). Describe how data will be stored to safe-guard confidentiality. SickKids requires data to be stored behind 2 physical (i.e., a locked cabinet in a locked office) or 2 electronic (i.e., an encrypted file on a locked computer) locks. In addition, consider inclusion of the following information:*

* Describe how data/samples will be coded or unlinked.
* If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.
* If research data/samples will be coded, describe how access to the “key” for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.
* *Include a discussion of the circumstances in which data or samples will be shared with other researchers.*
* *If data is being transferred or linked to data from another institution(s), describe which institutions, how this will be done, and how confidentiality will be protected. Note that identified data cannot be transferred outside of the institution without participant consent.*
* *Include a discussion of plans to publish participant’s family pedigrees, with a description of measures to minimize the chance of identifying specific families.*
* *Describe any situations in which personally identifiable information will be released to third parties.*
* *State who has access to records, data, and samples. Consider if monitors or auditors outside of study Investigators will need access.*
* *Discuss any additional features to protect confidentiality and approaches to ensure privacy of study participants.*

[Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name, only by unique study ID number. The patient’s name or any identifying information will not appear in any reports published as a result of this study. All identifying information will be kept behind 2 security measures or as per equivalent institutional policy, under the supervision of the study/site PI and will not be transferred outside of the hospital.

The study monitor, auditor and other authorized representatives of the Sponsor, representatives of the Research Ethics Board (REB), regulatory agencies or <company name> supplying study product (if contractually required) may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.]

<Insert text>

### Future Use of Stored Specimens and Data

*If intended specimens or residual specimens are retained after the study is complete, include the provisions for consent and the options that are available for the participant to agree to the future use of his/her specimens, images, audio or video recordings. Describe if sample collection and storage for future use is optional or mandatory. Specify the location(s), if other than the clinical site, where specimens or other data will be maintained, how long specimens or other data will be stored, if the site's REB will review future studies, and protections of confidentiality for any future studies with the stored specimens or data (e.g., specimens will be coded, bar-coded, de-identified, identifying information will be redacted from audio recording transcripts). Include a statement that genetic testing will or will not be performed.*

*See also* ***Section 10.1.2, Confidentiality******and Privacy*** *and* ***Section 10.1.8, Data Handling and Record Keeping****, for further information on future use of study records.*

[Data collected for this study will be analyzed and stored at the <specify name of Data Coordinating Center >. After the study is completed, the de-identified, archived data will be transmitted to and stored at the <specify name of Data Repository>, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

With the participant’s approval and as approved by local Research Ethics Boards (REBs), de-identified biological samples will be stored at the <specify name of Biosample Repository> with the same goal as the sharing of data with the <specify name of Data Repository>. These samples could be used to research the causes of <specify condition(s)>, its complications and other conditions for which individuals with < specify condition(s)> are at increased risk, and to improve treatment. The <specify name of Repository> will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the <specify name of Repository>.]

<Insert text>

### Key Roles and Study Governance

*Provide the name and contact information of the Principal Investigator and the Medical Monitor, if applicable.*

|  |  |
| --- | --- |
| **Principal Investigator** | **Medical Monitor** |
| Name, degree, title | Name, degree, title |
| Institution Name | Institution Name |
| Address | Address |
| Phone Number | Phone Number |
| Email | Email |

*Describe the role of the Medical Monitor in the trial. A Medical Monitor is a physician with research and therapeutic expertise who is not directly seeing, treating or conducting research on the participants, but who provides medical expertise and safety oversight. The Medical Monitor should be involved throughout the development of the protocol (e.g., trial design, inclusion and exclusions criteria, safety assessments and reporting, discontinuation criteria), during study conduct (e.g., assessment and reporting of adverse events and protocol deviations, dose escalation and modifications, participant discontinuation) and trial closeout and reporting.*

*In addition, briefly describe any study leadership committees (e.g.: Steering Committee, Executive Committee, Subcommittee) and their roles. Note that it is not necessary to list specific members. Also, describe country-specific administrative requirements or functions that materially affect the conduct of the study. The MOP should include a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.*

<Insert text>

### Safety Oversight

*All clinical trials must have a written plan to assess safety concerns and protect participants; the details of the safety monitoring plan should be described in this section. The safety monitoring plan could include the involvement of a Safety Monitoring Committee (SMC)[[1]](#footnote-2), Data Safety Monitoring Board (DSMB)[[2]](#footnote-3), and/or an Independent Safety Monitor (ISM)[[3]](#footnote-4). Independent oversight is an important component to ensure human subjects’ protection and data integrity and should be considered for each study. In this section, the type of safety oversight should be clearly identified along with any known responsibilities for the oversight of safety and data integrity in the study. If included for the study, describe the composition of the SMC or DSMB, frequency of interim data review, final data analysis and method of reviews. A separate DSMB Charter will provide further detail of DSMB membership, responsibilities and administration of the DSMB.*

[Safety oversight will be under the direction of a Data Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including <list expertise>. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to <specify the study Sponsor/other>.]

<Insert text>

### Study Monitoring

*Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).*

*This section should give a general description of how monitoring of the conduct and progress of the clinical investigation will be conducted (i.e., who will conduct the monitoring, the type, frequency, and extent of monitoring, who will be provided reports of monitoring, if independent audits of the monitoring will be conducted). This section may refer to a separate detailed study monitoring plan.*

*Investigator initiated Health Canada regulated trials, consult with Clinical Research Services for trial Monitoring at* [ask.CRS@sickkids.ca](mailto:ask.CRS@sickkids.ca)*​.*

[Monitoring of the trial will be performed to verify that:

* The rights and well-being of participants are protected;
* The reported trial data are accurate, complete, and verifiable from source documents; and
* The conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and local regulations and requirements.

The Sponsor will be responsible for all monitoring activities. Any trial-related duty or function transferred to and assumed by a third party, including monitoring and auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The monitoring plan for the trial will be documented prior to the activation of the study and include the following;

* Follow risk-based practices,
* Document the rationale for the chosen monitoring strategy,
* Reference the Sponsor’s process that will be followed to address situations of non-compliance,
* Describe the monitoring responsibilities of all the parties involved, and
* Outline the data and processes to be monitored.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of monitoring by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during monitoring visits and inspections, and that sufficient time is devoted to the process.

Monitoring procedures will be implemented beginning with the data entry system and data checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Monitoring reports will be issued after each monitoring visit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.]

<Insert text>

### Quality Assurance and Quality Control

*This section will briefly describe the plans for quality management, the system for assessing the quality of the clinical trial. Quality management encompasses quality assurance (QA)[[4]](#footnote-5) and quality control (QC)[[5]](#footnote-6).*

*Each site, both clinical and laboratory, should have SOPs for quality management that describe:*

* *How data and biological specimens (when applicable) will be evaluated for compliance with the protocol, ethical standards, regulations, and accuracy in relation to source documents.*
* *The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*
* *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).*
* *Staff training methods and how such training will be tracked.*
* *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*

*Regular monitoring and an independent audit, if conducted, must be performed according to ICH GCP. See also* ***Section 10.1.6, Study Monitoring****.*

[Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Auditing of the trial will be performed independently from monitoring to evaluate trial conduct and compliance with the protocol/amendment(s), SOP, ICH GCP and local regulations and requirements*.*

The Sponsor will be responsible for all auditing activities. Any trial-related duty or function transferred to and assumed by a third party, including auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of auditing by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during audits and inspections, and that sufficient time is devoted to the process.

Auditing reports will be issued after each audit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.]

<Insert text>

### Data Handling and Record Keeping

*Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. Describe in this section who will have access to records and a description of the data handling and record keeping for the conduct of the trial.*

#### Data Collection and Management Responsibilities

*Provide details regarding the type(s) of data capture that will be used for the study and any relevant data standards or common data elements that are being utilized as a part of the trial. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Further details should be provided in the MOP or the data management plan, including detailed descriptions of source documentation, CRFs, instructions for completing forms, data handling procedures, and procedures for data monitoring.*

*Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Electronic source data are data initially recorded in electronic form. Examples of source data include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants’ memory aids or evaluation checklists, pharmacy dispensing records, audio recordings 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 clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.*

*It is not acceptable for the CRF to be the only record of a participant’s inclusion in the study. Study participation should be captured in a participant’s medical record. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.*

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

*Provide a list of planned data standards, formats, terminologies and their versions, used for the collection, tabulation and analysis of study data.*

[Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator 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.

Where the source data is not collected as part of the participant’s medical record, hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on 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.]

<Insert text>

#### Study Records Retention

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

*Studies that fall under Health Canada Division 5 regulation, SickKids and/or Canadian sites only:*

[To enable evaluations and/or audits from Health Canada and/or the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition in a secure location for a minimum of 25 years.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.]

*Investigator initiated, multi-center, international trial:*

[To enable evaluations and/or audits from Regulatory Authorities, the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing REB, Institutional policies, the countries regulatory requirements or Sponsor requirements as specified in the Clinical Trial Agreement, whichever is longer.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor. The Principal Investigator must obtain the Sponsor’s written permission before disposing of any records.]

*Non-regulated trials:*

[To enable evaluations and/or audits from the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition in a secure location for a minimum of 7 years in accordance with SickKids policy.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.]

<Insert text>

### Protocol Deviations

*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. Refer to ‘*[Reporting of Unanticipated Problems (UP) including Serious Adverse Events and Protocol Deviations by Investigators to the SickKids Research Ethics Board’](http://my.sickkids.ca/research/clinical-research-services/Documents/Ethics%20Documents/Guidance-UnanticipatedProblems-SeriousAdverseEvents-ProtocolDeviations.pdf)*.*

[A protocol deviation is any noncompliance with the clinical trial protocol or Manual of Procedures (MOP) requirements, if applicable. The Principal Investigator 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), except where necessary to eliminate an immediate hazard(s) to the trial participants. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All protocol deviations will be documented; the Principal Investigator will assess each protocol deviation to determine the impact to the patient’s rights, safety or welfare, study efficacy and data integrity. If there is any uncertainty regarding the impact of the protocol deviation, the Principal Investigator will consult with the Medical Monitor.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within <specify number> working days of identification of the protocol deviation, or within <specify number> working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Sponsor. Protocol deviations must be sent to the reviewing REB in accordance with their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing REB requirements.]

<Insert text>

### Conflict of Interest Policy

*This section should include a description of how the study will manage actual or perceived conflicts of interest.*

[The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Hospital for Sick Children has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.]

<Insert text>

## Additional Considerations

*This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or REB-related requirements.*

<Insert text>

## Abbreviations

*The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).*

|  |  |
| --- | --- |
| AE | Adverse Event |
| ADR | Adverse Drug Reaction |
| ANCOVA | Analysis of Covariance |
| CIOMS | Council for International Organizations of Medical Sciences |
| CLIA | Clinical Laboratory Improvement Amendments |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| eCRF | Electronic Case Report Forms |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| IB | Investigator’s Brochure |
| ICH | International Council on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IND | Investigational New Drug Application |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |
| LSMEANS | Least-squares Means |
| MOP | Manual of Procedures |
| MRP | Most Responsible Physician |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| PHIPA | Personal Health Information Protection Act |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SoA | Schedule of Activities |
| SOP | Standard Operating Procedure |
| SUADR | Serious unexpected adverse drug reaction |
|  |  |

# REFERENCES

*Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer’s IB, package insert, and device labeling.*

*Examples:*

* ***Journal citation*** *Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.*
* ***Whole book citation*** *Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.*
* ***Chapter in a book citation*** *Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.*
* ***Web Site citation****Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.*
* ***Electronic Mail citation***

*Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]*

* ***References to package insert, device labeling or Investigator’s Brochure***

*Cite date accessed, version number, and source of product information.*

1. A Safety Monitoring Committee (SMC) is a small group of experts with at least two members who are independent of the protocol who review data from a particular study. Generally, independent investigators and biostatisticians should be included. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, intervention, and target population under study. [↑](#footnote-ref-2)
2. A Data Safety Monitoring Board (DSMB) is an independent group of experts that advises funding IC(s) and the study investigators. The members of the DSMB provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, intervention, or target population under study. [↑](#footnote-ref-3)
3. An Independent Safety Monitor (ISM) is a physician, nurse, or other individual with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of Adverse Events, immediately after they occur or are reported, with follow-up through resolution. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study. [↑](#footnote-ref-4)
4. All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with ICH GCP and the applicable regulatory requirement(s) (ICH E6 Section 1.46). [↑](#footnote-ref-5)
5. The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled (ICH E6 Section 1.47). [↑](#footnote-ref-6)