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STATEMENT OF COMPLIANCE

This trial is being conducted under a Clinical Trial Application (CTA) which is ongoing with Health Canada. The trial will be conducted in accordance with Good Clinical Practice (GCP) as described in Health Canada's section C.05.010/Division 5 of the Food and Drugs Regulations, International Conference on Harmonization-Good Clinical Practice (ICH-GCP E6 R2), and Tri-Counsel Policy Statement (TCPS2, 2014), applicable federal, provincial and local regulatory and legislative requirements.

The Sponsor-Investigator, Dr. Alex Aregbesola, will assure that no deviation from, or changes to the protocol will take place without prior documented authorization (i.e., a no objection letter - NOL) from Biomedical Canada (Therapeutic Products Directorate) and documented approval from the University of Manitoba (UoM) Health Research Ethics Board (BREB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed the required mandatory compliance training.

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to UoM BREB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the UoM BREB before the changes are implemented to the study as well as authorization from Health Canada. All changes to the consent form will be BREB approved.

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PROTOCOL SUMMARY

Title:	Using a single dose of dexamethasone at 0.6mg/kg of body weight versus 0.15 mg/kg of body weight for the treatment of croup: an internal vanguard randomized controlled non-inferiority trial.
Sponsor	The University of Manitoba
Sponsor-Investigator	Dr. Alex Aregbesola
Study Description:	We will conduct an internal vanguard, randomized, double-blind trial comparing treatment with dexamethasone at 0.15mg/kg to 0.6mg/kg for children with croup.
Objectives:	-To determine a feasible sample size estimation, eligibility criteria, recruitment and retention rates and the noninferiority margin for the definitive RCT. -Engage patients and families with lived experience to improve the vanguard RCT and to support designing and implementing the definitive RCT.
Outcomes:	**Primary outcome**: -Return visits or readmissions to the hospital within 7 days following initial presentation to the ED with croup. **Secondary Endpoints**: -Adverse events (AEs) following treatment with either of the 2 doses of dexamethasone within 7 and 30 days of treatment. AEs: Disseminated varicella, gastrointestinal bleeding, unspecified bleeding, pneumonia, sepsis, febrile convulsion, bacteria tracheitis, tachycardia/fast heartbeat, and restlessness.
Study Population:	We will enroll 50 children at the Winnipeg Children's Hospital ED. We will enroll children aged 6 months – 5 years with clinical diagnosis of croup within the next 1 year. We will exclude children who are unable to tolerate or ingest oral dexamethasone, other causes of stridor, other underlying systemic diseases defined as chronic lung disease, chronic heart disease, chronic kidney disease, and immunodeficiency), recent exposure to varicella, treatment with oral or intravenous corticosteroids within the preceding 72 hours.
Phase:	Vanguard
Description of Sites/Facilities Enrolling Participants:	Health Sciences Centre Winnipeg Children's Hospital (Winnipeg),
Description of Study Intervention:	Active Intervention: Treatment with one dose of oral dexamethasone (0.15 mg/kg per dose; maximum single dose 3 mg) Active control: Treatment with one dose of oral dexamethasone (0.6 mg/kg per dose; maximum single dose 12 mg)
Study Duration:	Estimated time 12 months from when the study opens to enrolment until completion of data analyses.
Participant Duration:	Participants will be followed up when presenting to the ED within 7 and 30 days after their enrolment visit.

SCHEDULE OF ACTIVITIES

Procedures	Enrollment Visit (Day 0)	4 hours post oral intervention or at discharge (if sooner than 4 hours)	Day 1 - 7	Day 8 - 30	Day > 30
Screening	X				
Inclusion/exclusion criteria	X				
Informed consent	X				
Demographics	X				
Medical history	X				
Vital signs	X	X			
Weight	X				
Allocation	X				
Adverse event monitoring and determination	X	X	X	X	
Chart review/electronic data base review					X
Complete Baseline Case Report Forms (CRFs)	X	X	X		
Complete follow up CRFs			X	X	
Oral dexamethasone 0.15mg/kg vs 0.6mg/kg	X				

INTRODUCTION

Croup is a common childhood respiratory disease that leads to frequent emergency department (ED) visits (1). **It accounts for 7% and 3% of hospitalization in under 5 and children between 6 months-3 years in North America, respectively (2, 3).** The diagnosis of croup is clinical including sudden onset of a seal-like barking cough, often accompanied by stridor, voice hoarseness, and respiratory distress (1). While croup is a self-limiting viral infection, the burden of frequent hospitalization contributes significantly to health care utilization (4, 5). Studies have reported on the effectiveness of glucocorticoids at reducing the severity of croup, the rate and length of hospitalization, return visits, and admission to the intensive care unit for croup (6-8). However, they are associated with adverse events (AEs) (9-12).

RATIONALE

Adverse events**:** A recent self-controlled case series study with over **4 million children** examined the potential harms of corticosteroid bursts (defined as courses of oral corticosteroids for 14 or fewer days) (9) and found that the most common indications for prescription of corticosteroid bursts were acute respiratory tract infections (including croup syndrome) and allergies (9). Of the AEs investigated, **GI bleeding, pneumonia, and sepsis (including bacteria tracheitis)** were directly associated with glucocorticoid bursts. The incidence rate differences per 1000 person-years between children administered a single corticosteroid burst and those not prescribed corticosteroids were 0.60 (95%CI, 0.55-0.64) for **GI bleeding**, 9.35 (95%CI, 9.19-9.51) for **pneumonia,** and 0.03 (95%CI, 0.02-0.05) for **sepsis**. Likewise, another case-control study (10) that was not statistically significant but clinically relevant sounded a note of caution on a possible increase in cases of **disseminated/complicated varicella zoster infection** with recent corticosteroid use.

Bronchopneumonia and bacteria tracheitis have been reported in patients treated with dexamethasone at 0.6mg/kg versus 0.15mg/kg in a randomized controlled trial (RCT) (11). Parker et al. (12) reported increased vomiting and febrile convulsion with dexamethasone at 0.6mg/kg. To date, the trials that reported on the AEs associated with using dexamethasone at 0.6mg/kg are limited, inconclusive, **but suggest that a low dose may be associated with fewer AEs** (11-15). All the RCTs were based on the frequentist approach (11-15), **which is prone to error of misinterpretation**. Bayesian methods are an alternative to the frequentist, i.e., the standard null hypothesis significance testing (NHST) framework, and they have advantages.

Glucocorticoids: Glucocorticoids are a class of corticosteroids with anti-inflammatory properties through which they reduce the mucosal edema and inflammation that characterize croup and, as such, reduce the associated difficulty in breathing (7). Dexamethasone is one of the long-acting systemic corticosteroids with a high glucocorticoid potency (15). A few systematic reviews have been conducted on the effectiveness of treating croup with glucocorticoids (16-19). **We just published a Cochrane systematic review (20) to address the growing debate about the effectiveness of low dose glucocorticoids to treat croup** (9, 11-14). We found that a smaller dose of dexamethasone at 0.15 mg/kg is as effective as the standard dose of dexamethasone at 0.60 mg/kg. **We also found no significant difference in return visits or readmissions** of croup patients treated with either of the doses (**relative risk [RR]=0.91, 95% CI**

0.71 to 1.17). Likewise, there **was no significant difference in length of stay in the hospital or ED (mean difference [MD]=0.12, 95% CI −0.32-0.56)** (20). While a few studies have compared dexamethasone at 0.6 mg/kg to 0.3mg/kg, the call to investigate dexamethasone at 0.15mg/kg of body weight is more common (14, 20). **It is clinically relevant to know the lowest dose of dexamethasone that treats croup effectively.**

Bayesian methods**:** Bayesian methods are increasing in clinical research and are particularly useful in conducting and analyzing RCTs (21, 22). This is partly due to concerns about the interpretation of results based on the NHST framework, which is prone to error (21) and susceptible to misinterpretation (23). A body of evidence have relentlessly highlighted the limitations and misconceptions of the NHST framework and *P*-values (24, 25), including interpreting a non-statistically significant difference (*P*-value >5%) between two groups to mean that the null effect is most likely. **Bayesian methods also allow the incorporation of external information into the design and analysis of the trial, this is especially important during the design phase where sample size calculations require information on effect sizes and variability** (26). Expert elicitation is one method to extract this prior knowledge and is becoming more frequent in trials. A review of 460 studies that discussed Bayesian prior elicitation found 42 studies related to clinical trial design and analysis (27). ***Expert elicitation aims to come to a clinical consensus about the current information available about the outcome of interest, encoded in a "prior distribution". Prior distribution can be used in Bayesian sample size estimation while accounting for statistical uncertainty.***

Patient engagement: Engaging patients with lived experience in designing and implementing RCTs is of immense benefits. There is an increase in recognition of patient experience as one of the indicators of quality healthcare (28, 29). Evidence suggests a direct association between a good patient experience and optimal care and patient safety (30). In pediatric EDs where the diversity of patients is increasing, a shared model is especially important. None of the previous RCTs that compared the two doses considered patient voice or reported on patient engagement in designing or implementing the trial.

HYPOTHESIS

1. Implementing a Bayesian elicitation process alongside a vanguard RCT will provide a strong basis to design a definitive noninferiority RCT of dexamethasone at 0.15mg/kg. 2. Engaging patients/parents with lived experience will help to (ensure the vanguard RCT is as best as possible for participants and) identify priority areas for families in implementing the definitive RCT.

RESEARCH QUESTION

1. Is the definitive RCT feasible based on eligibility criteria and the recruitment process in the vanguard RCT? 2. Based on a Bayesian elicitation process, what sample size is needed for the definitive RCT to assess noninferiority of dexamethasone at 0.15mg/kg versus 0.6mg/kg using a Bayesian framework? 3. What is the noninferiority margin of treating croup with 0.15mg/kg that can be tolerated by clinicians? 4. What are the priorities of families in assessing noninferiority of dexamethasone at 0.15mg/kg versus 0.6mg/kg to treat croup?

OVERALL GOAL

The overall goal is to reduce the AEs associated with the treatment of croup by using a low dose of dexamethasone at 0.15mg/kg. The specific objectives below will help in achieving this goal.

SPECIFIC OBJECTIVES

The specific objectives of the studies described in this application are:

1. Implement a vanguard RCT to determine a feasible sample size estimation, eligibility criteria, recruitment and retention rates and the noninferiority margin for the definitive RCT.
2. Engage patients and families with lived experience to improve the vanguard RCT and to support designing and implementing the definitive RCT.

METHODS AND EXPERIMENTAL APPROACHES

Design and study site:

This is an internal double-blinded vanguard RCT, which will be conducted at the Winnipeg Children's Hospital (WCH). **The entire project is designed to plan and implement a large multi-center definitive RCT** (31). The timeline and research activities of the entire study are presented in **Table 1 and Figure 1**.

Phase 1: Obtaining ethics approval.

We will obtain ethics approval from all relevant regulatory bodies. **Table 1** shows the list of the bodies.

Phase 2a: Implementing an internal vanguard RCT at WCH to plan and design a multicenter definitive RCT.

The vanguard RCT aims to assess **a feasible sample size, eligibility criteria, recruitments rates, and noninferiority margin for a definitive RCT**.

Inclusion criteria:

These are:

-Children aged (**6 months-5 years**) with clinical diagnosis of croup (1, 32).

-Presenting to the Winnipeg Children's Hospital ED

Exclusion criteria:

These are:

-Children with body weight more than 20kg

-Children who are unable to tolerate or ingest oral dexamethasone,

-Known hypersensitivity/allergy to dexamethasone,

-Other causes of stridor (such as acute epiglottitis, bacterial tracheitis, anaphylaxis, foreign body aspiration),

-Other underlying systemic diseases defined as chronic lung disease, chronic heart disease, chronic kidney disease, and immunodeficiency),

-Recent exposure to varicella,

-Treatment with oral or intravenous corticosteroids within the preceding 72 hours.

Description of Study Intervention and Outcome

The intervention is dexamethasone at 0.15mg/kg while the active control is dexamethasone at 0.6mg/kg. The primary outcome is return visits or readmissions to the hospital within 7 days following initial presentation to the ED with croup. The secondary outcome is AEs following treatment with either of the 2 doses of dexamethasone within 7 and 30 days of treatment (Appendix A).

Risks

The risks participants of this study may be exposed to are risks related to the use of dexamethasone for clinical care of children with croup. Participant's assigned group may end up being less effective or have more side-effects that the other group. Participants assigned to receive 0.15mg/kg may be at risk for incomplete response compared to those in the active control group. The study will not involve any change from the way the child would have been treated and/or managed if not participating in the study. AEs such as GI bleeding, pneumonia, sepsis including bacteria tracheitis have been associated with glucocorticoid bursts. Additional risk may arise relating to the collection of personal health information. However, there are measures in place to keep these risks as minimal as possible.

Lifestyle modification**:** This is not applicable.

Screen failure:

Eligible participants will be screened at triage as part of standard care for any clinically significant known hypersensitivity to dexamethasone and/or excipients, OraBlend citrus or OraBlend citrus sugar free. As a form of quality check, we will screen all enrolled participants to confirm they were appropriately screened for eligibility at time of enrollment. We will re-assess the patients' sex, age (months), eligibility criteria, and consent status. This second level of screening is to allow reporting according to the non-inferiority CONSORT guidelines (33). Patients will not be rescreened within the same ED visit but will be rescreened on subsequent ED visits for the same croup episode.

Vanguard RCT recruitment process and sample size estimation:

Based on the budget allocated for patient recruitment (**see attached budget),** sampling of children with clinical diagnosis of croup who presented to the WCH ED between January 2021 and January 2022 (**n=710**), and our experience from a similar trial that used 720 children (34), we plan to recruit 50 children within a year for this vanguard trial (Figure 1). **We will enrol 50% (25 children, in ratio 60:40% male to female) per treatment arm and assess for missing data and protocol adherence.** We will leverage a Bayesian elicitation process used by our team for an ongoing trial on bronchiolitis (35). We will elicit the probability of return visits or readmissions to ED within 7 days for each dose of dexamethasone at 0.15mg/kg versus 0.6mg/kg. The probabilities of revisits or readmissions to the ED closely reflect clinical decision making. We will then use bivariate elicitation to understand the relationship between the two probabilities (36, 37).

Dexamethasone oral preparation:

The dexamethasone suspension base consists of 1mg/mL oral suspension of dexamethasone with citrus flavored syrup. Dexamethasone 0.25mg/ml oral suspension will be compounded for intervention group. Dexamethasone 1mg/ml oral suspension will be compounded for the control group. To aid blinding, the preparations will be compounded and pre-packaged in identical bottles by the Pharmacy. The preparations will not be distinguishable by appearance, volume, weight, taste, or smell and will be packaged in identical bottles sequentially numbered, sealed, and delivered in opaque bags. **The intervention group will receive oral dexamethasone at 0.15mg/kg (maximum dose 3mg). The active control group will receive oral dexamethasone at 0.6mg/kg (maximum dose 12 mg).** Patients will be observed for 30 minutes, if diagnosed with mild croup, and 4 hours if diagnosed with moderate or severe croup, and if vomiting occurs, one additional dose will be administered**.**

Recruitment, blinding, and withdrawal:

Potential participants will be screened and enrolled consecutively after obtaining consent (**Appendix C, Appendix D and Appendix E**). Blinded parties will include the participant, caregiver, research nurse, research assistant, study coordinator, outcome assessors and principal investigators. The research nurse/research assistant will perform recruitment, consent and maintain the master list. Participants will be able to withdraw from the study at any time upon request. However, data accrued from the participant to the time of withdrawal will be retained for analysis. We have designed the baseline and follow-up case report forms (CRFs) (**Appendix F and Appendix G**) to capture the data to be developed in REDCap. We will follow the standard accepted method of reporting noninferiority RCT (42). We have developed a pharmacy manual (Appendix H) with monographs (Appendix I) and manual of operation (MOP – Appendix J) to help guide this study.

MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization

Computerized randomization will be performed by a statistician at the George and Fay Yee Centre for HealthCare Innovation to generate the randomization list. We will perform a computerized randomization in REDCap stratified by age (Figure 1). We will do a block randomization with random

blocks of undisclosed block sizes over the seasons to ensure that we get temporal distribution of croup cases. We will randomly assign patients into either the intervention or control in ratio 1:1. This process will help to reduce bias due to selection and residual confounding that may bias our results. Because croup season peaks over the fall and winter months in Canada, our randomization will consider this factor such that each arm will have an almost similar number per the peak season. While croup is common between 6 months and 5 years, a typical croup affects children between 6 months and 3 years. Based on this, we will randomize such that this age category (6 months-3years and >3 years – 5 years) has almost similar distribution in each arm.

Sequence Generation

A statistician (not otherwise involved in the study) at the George and Fay-Yee Centre for HealthCare Innovation will develop and maintain a computer-generated permuted-block randomization list, stratified by age. The randomization list will be sent to Pharmacy, where the list will be used to compound and label pre-packaged bottles numbered sequentially.

Allocation concealment

To ensure concealment, dexamethasone for the two groups will be packaged in an identical manner. The dexamethasone suspension base consists of either 1mg/mL oral suspension or 0.25mg/ml of dexamethasone with citrus flavored syrup. The preparations will not be distinguishable by appearance, volume, weight, taste, or smell and will be packaged in identical bottles sequentially numbered, sealed, and delivered in opaque bags. In the case of an emergency, participant's allocation will be unblinded.

Masking Procedures

All study personnel (including study coordinators, research nurse, research assistant, investigators) and patients/families will be blinded to the study group assignment. The pharmacists and statistician will be aware of participant assignment but will not be involved with research activities (participant enrolment, data collection, data entry or follow-up).

Details of allocation concealment are outlined above.

Unblinding Procedures

Data Safety Monitoring Board (DSMB): The DSMB may request unblinding if they deem it necessary to consider the results of the interim safety analysis or to review possible AEs. The DSMB may also request the pharmacist to reveal the patient's group allocation to examine possible adverse events.

Urgent unblinding: In the event of an emergency, unblinding will be performed upon request. The pharmacist, who will maintain the randomization list, will be sent the kit number dispensed to help determine the dose of dexamethasone received by the patient. As the Investigational Drug Service (IDS) Pharmacy hours are Monday to Friday 0800 – 1600H, code break outside of regular working hours will be performed by Pediatric Intensive Care Unit (PICU) Pharmacy. IDS Pharmacy to send the final randomization list to PICU Pharmacy to assist with unblinding requested outside IDS Pharmacy hours. All instances of unblinding will be documented (including reason for unblinding; SAEs,

protocol deviation, etc.) and reported to the University of Manitoba Biomedical Research Ethics Board, the Research Service of Shared Health and Health Canada. Circumstances that may require urgent blind breaking would include clinical symptoms that could be related to the study medications (such as evidence of gastrointestinal bleeding and febrile convulsion). Any unblinding decision will be considered an unanticipated problem and as such will be documented and reported to the DSMB. The plan for treating clinicians to change or stop treatment with either of the two doses will not warrant breaking of the study blind but will result in stoppage or changing of the patient's medication. Following locking of the database and completion of the primary analysis the statistical team will be unblinded.

STUDY ASSESSMENTS AND PROCEDURES

Efficacy Assessments

Baseline Measurements: Data regarding age, sex, weight, date of presentation, croup severity, symptoms at ED presentation, onset of symptoms, length of ED stay, discharge date, hospitalization due to croup, length of hospitalization, dose of dexamethasone, other medications (such as epinephrine, antibiotics) and the doses administered, will be collected at baseline and recorded in the Baseline CRF. We also estimate eligibility criteria and recruitment rate.

Measurements in the ED:

Patients will have vital signs such as temperature, respiratory rate, heart rate, and oxygen saturation measured prior to receiving their oral study medication (time 0). Blood pressure will be measured at enrolment when possible (blood pressure measurements can be difficult to obtain in crying infants). Triage ED temperature measurement (rectal, otic, temporal or axillar) will be used as the baseline temperature. The research nurse will record measurements on in the baseline CRF. Information regarding side effects, co-interventions, length of stay and disposition will be recorded throughout the intervention period in the ED. Patients will be monitored for 30 minutes if mild croup or 4 hours if moderate or severe croup following administration of the oral medication or until discharge (whichever is first) after the first study medication.

Follow-up measurement in the ED:

The participants' parents/caregivers will not be followed up by either email or telephone following enrolment. However, the outcome assessors will collect data from patient's electronic medical records (EMR) per the follow-up CRF. The follow-up data will include date of initial presentation to ED, date of discharge at initial presentation to ED, number of return visits to the ED with 7 and 30 days, croup severity, symptoms at ED presentation, onset of symptoms, length of ED stay, discharge date, hospitalization due to croup, length of hospitalization, dose of dexamethasone, other medications (such as epinephrine, antibiotics) and the doses administered, AEs associated with the medications, will be collected at follow visits and recorded in the Follow-up CRF. We will also estimate the retention rate.

Chart Review: A research team member will review each participant's hospital chart once the 30-day follow-up period has elapsed to examine return ED visits, admission to hospital, diagnosis for any hospital visit, any corticosteroid treatment in hospital. All children with an admission diagnosis of croup will be considered to have been admitted for croup. All charts where an admission diagnosis is other than croup will be reviewed by the site coordinator in conjunction with qualified site investigator to determine reason for admission. We will define admission to hospital as per ICD-10 (Appendix A).

Phase 3: Patients' engagement in designing and implementing the vanguard RCT.

We will **engage 6 patient partners (in this case parents) from our existing patient partner network at CHRIM with lived experience of bringing a child with croup to the WCH ED and other centers (Innovation 2)**. One of the patient partners will be embedded in the research team, joining monthly meetings to ensure the patient voice is considered throughout the process. There are no anticipated physical risks for parents/care providers of croup patients. However, asking questions about their experience with children who had croup may be traumatic and emotionally challenging. As such, we will monitor symptoms of emotional trauma such as agitations, nervousness, anxiety, headache and crying spells. We will provide support numbers and organizations should any of the patients need any form of help while participating in this study.

Year 1: To plan for this study, we collected Snarr's experience with her two children who had croup. We know from these conversations with Snarr that specific symptoms are more bothersome and worrisome for families than others, so we want to ensure that we are tracking these particularly. The ideas that come up will be incorporated into data analysis and interpretation plan of chart review, including giving input on how to use and share this data and what results to prioritize for the vanguard RTC.

YEAR 2: Patient partners review and provide comments on the consent forms, scripts, and other documents that will be used to approach patients for recruitment into the definitive RCT. The researchers will continually consult with patients through Snarr, attending monthly and three dedicated family partner meetings. We want to ensure research questions reflect patient priorities, the methods work for the patient population, and that patient facing documents are appropriate. The family partners will also support grant writing for the definitive RCT.

YEAR 3: The family partners will support the vanguard RCT as needed, interpret the data as it becomes available and support grant writing for definitive RCT to ensure family priorities are considered.

Definitive RCT:

Our PICO criteria for the definitive trial as well as the design including the sample size and the proportion of patients to be enrolled in the intervention and control will be based on the findings from the Bayesian elicitation exercise and recommendation from patients with lived

experience. However, we know that our **PICO** would be the same as the vanguard RCT.

Adverse Events and Serious Adverse Events

Definition of Adverse Events: As per GCP, the definition of an **AE** is as follows: "Any **untoward** medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment." GCP defines an **Adverse Drug Reaction (ADR)** as: "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. "

Definition of Serious Adverse Events: A **Serious Adverse Event** (**SAE**) and a **Serious Adverse Drug Reaction (SADR**) will be defined as any **untoward** medical occurrence that:

-results in death.

-is considered a life-threatening event (patient at imminent risk of death);

-results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

-prolongs an existing hospitalization; and

-is an Important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered serious when, based upon appropriate medical judgment of the qualified site investigator, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Classification of an Adverse Event: All AEs will be classified according to ***MedDRA*** (**Med**ical **D**ictionary for **R**egulatory **A**ctivities) – a multilingual standardized international medical terminology dictionary used for "regulatory communication and evaluation of data pertaining to medicinal products for human use."[117]

Severity of Event

All AEs will be assessed by the qualified site investigator and the following guidelines will be used to describe severity.

-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. 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.

Relationship to Study INTERVENTION

All AEs will have their relationship to study intervention assessed by the Qualified Site Investigator who examines and evaluates the participant based on temporal relationship and

his/her 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 occurs in a plausible time relationship to study intervention administration and cannot be explained for example, by concurrent disease or other drugs or chemicals.

-Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed for example to concurrent disease or other drugs or chemicals.

-Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

-Unlikely to be related – A clinical event 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).

-Not Related – The AE is completely independent of study intervention administration, and evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness

The Qualified Site Investigator will be responsible for determining whether an AE/ADR is expected or unexpected. An AE/ADR 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. An unexpected ADR reaction will be defined explicitly as: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Time Period and Frequency for Event Assessment and Follow-Up

AEs will be collected from the time the participant is consented until the participant has completed the study. The occurrence of an AE or SAE may come to the attention of study personnel during the ED enrolment visit, during the ED chart review, by a participant's caregiver contacting the study team, or finally by review by a study monitor. SAEs that could be related to dexamethasone (Appendix A) will be specifically solicited from participants' parents/caregivers on revisits. Participants will be followed for 30 days from the date of enrolment for adverse events.

All AEs will be captured on the follow-up CRF in REDCap. Information to be collected includes

an event description, date of onset, clinician's assessment of severity, relationship to study product (assessed by the qualified site investigator), and date of resolution/stabilization of the event and event outcome (resolved/recovered, recovered with sequelae, not recovered/not resolved, death and unknown. All AEs will be followed to adequate resolution or until the Qualified Site Investigator deems the event to be chronic or the participant has been deemed clinically stable.

Adverse Event Reporting

MOP has been developed to ensure that all AEs are reported in a timely manner. The MOP will describe staff responsibility for completing and signing off on the AE reports, who will receive notification of AEs, and who is responsible for meeting site REB and regulatory requirements. AEs will be tabulated and reported to the DSMB and UoM HREB. Expected SAEs/SADR and unexpected SAE/SADR will be reported.

Croup disease-related events:

Disease related events that are not concluded to be related to the study drug by the Site Qualified Investigator and are part of the natural history of croup will not be reported as AEs (although they will be captured as part of study data collection):

- Hospitalization related to croup.
- The use of IV or NG rehydration for maintaining fluid balance related to croup.
- Cough, difficult breathing.
- Apnea.
- Intensive care admission related to croup; and
- Use of respiratory supports (such as supplemental oxygen, high flow nasal cannula, CPAP, and intubation/mechanical ventilation) in the treatment of croup.

Pre-existing medical conditions:

The deterioration, worsening or increase in frequency of a participant's pre-existing condition at any time during the study will be considered an AE.

Laboratory Results:

Laboratory results that are deemed clinically significant, as per the QI will be reported as an AE. For positive urine and blood cultures, we will utilize the following process. Urine and blood cultures that are more than 12 hours after time of patient enrollment and are positive should also be reported as an AE.

Serious Adverse Event Reporting

The Qualified Site Investigator will report any SAE, whether or not considered study intervention related, and any SADR to the Sponsor-Investigator within 72 hours of becoming

aware of the event. The Qualified Site Investigator will complete a "Serious Adverse Event/Drug Reaction Report Form". The Qualified Site Investigator will include an assessment of whether there is a reasonable possibility that the study intervention caused the event and whether the treatment was given, withheld, discontinued. Any additional requested information from the DSMB or Sponsor-Investigator should be completed as soon as possible. The site will report SAE/SADRs to UoM REB in accordance with the SAE/SADR reporting requirements. The Sponsor-Investigator will also inform the DSMB of the information provided from the site as soon as possible but no later than 7 days after the initial reporting.

If the SAE or SADR are also **unexpected**, the Sponsor- investigator will also file a Serious Unexpected ADR report with Health Canada:

- where the AE/ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information.
- where the AE/ADR is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
- within 8 days after having informed Health Canada of the SAE/SADR, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

In addition, the Sponsor-Investigator will notify the Site Investigator of SAE and SADR that are also **unexpected:**

- where the AE/ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information; and
- where the AE/ADR is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information.

Reporting Events to Participants

All caregivers of the study participants will be informed in a timely manner if information becomes available that may be relevant to the study participant's willingness to continue participation in the study.

Events of Special Interest: Not applicable.

Reporting of Pregnancy: Not applicable.

Unanticipated Problems

Definition of Unanticipated Problems

An Unanticipated problem (UP) is any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected regarding nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the REB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problem Reporting

The qualified site investigator will report UPs to the Sponsor- Investigator, the UoM HREB according to their reporting policies. The UP report will include the following information:

- Protocol identifying information: protocol title and number, Qualified Site Investigator's name, and the responsible HREB project/reference or case number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represent a UP; and
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs or SADRs will be reported to the Sponsor-Investigator, UoM REB, and DSMB according to the protocol.
- Any other UP will be reported to the Sponsor-Investigator within 15 days of the Qualified Site Investigator becoming aware of the problem and to the UoM HREB in accordance with their reporting guidelines; and
- All UPs will be reported to appropriate institutional officials (as required by an institution's written reporting procedures).

Reporting Unanticipated Problems to Participants

All caregivers of the study participants will be notified if at any time there are new UPs which may potentially impact willingness to continue participation in the study.

Data management and statistical analysis plan

We will use Beta distributions to represent the individual priors for the probabilities elicited based on the mode and 95% credible interval. The aggregate prior distribution from the individual level distributions will be found using the equal-weighted linear pooling method to reduce biases introduced by overoptimism and overconfidence (43, 44). For definitive RCT, we will determine the total required sample size using the Average Length (AL) criterion - a method for Bayesian sample size calculation (45). Based on that sample size, we will simulate the type I error and power to evaluate the efficiency of the definitive RCT.

We will present the number of responses and the percentage of patients who would prefer the use dexamethasone at 0.15mg/kg versus 0.6mg/kg. We will also present the reasons for their choice.

IMPACT/SIGNIFICANCE:

Implementing a vanguard RCT will help identify the potential challenges that may arise during a definitive RCT and, more importantly, an insight into how to mitigate the challenges. The success of this vanguard trial **will positively impact on cost and time needed for the definitive RCT**. Parental input in shared health decision-making is needed for quality health care. Locally, the Manitoba Quality and Learning framework (46) identifies patient experience and population health as two crucial aims.

EXPECTED OUTCOMES

Implementing remote, real-time expert elicitation will generate reliable and robust sample size estimation and reliable noninferiority margin. We expect differences in the priority of study outcomes between the investigators and patients with lived experience. We expect that this will provide the groundwork for a robust and comprehensive definitive RCT in Canada to determine whether 0.15mg/kg is noninferior to 0.6mg/kg to treat croup.

STRENGTHS AND LIMITATIONS:

This is the first RCT to implement the Bayesian elicitation process simultaneously with patient engagement to assess the noninferiority of dexamethasone at 0.15mg/kg versus 0.6mg/kg to treat croup. This is a vanguard RCT, which will provide a platform and experience for designing and implementing a definitive RCT. Our team has shown that remote, real-time expert elicitation is easy and cost-effective (35). Patient recruitment may be a challenge, but this can be addressed using our strong links to clinical trialists and our dedicated clinicians in Manitoba and Pediatric Emergency Research Canada (PERC).

KNOWLEDGE TRANSLATION (KT) AND MOBILIZATION PLAN

Existing KT platform:

We will disseminate the findings through the Translating Emergency Knowledge for Kids (TREKK) network, social media, newsletters, and national meetings. TREKK was created in 2011 as a national knowledge mobilization network through the Government of Canada's Networks of Centres of Excellence program to accelerate the speed at which the latest evidence in pediatric emergency care is put into practice (47). It has become a world leader in co-creating user-informed, high quality, evidence-based, impactful resources, including clinical tools (e.g., management algorithms, order sets, checklists), innovative parent tools (e.g., videos, ebooks, infographics) and 1–2-page summaries that share key issues and current, available evidence for managing acute pediatric illness **(>65,000 downloads from trekk.ca**) (48).

Integrated KT plan:

I have an established connection with TREKK. This network will help facilitate receiving feedback on the findings from the chart review and vanguard RCT. I also have an established

connection with the patient engagement team through whom I will receive feedback from the rest of the patient partners. The synergy between feedback received from health care providers and patient partners will ensure a shared model input in the definitive RCT. There will be presentations at provincial, national (PERC), and international conferences. Any feedback on this vanguard trial will be considered in designing and implementing the definitive RCT.

GENDER AND SEX-BASED ANALYSIS

There is a sex difference in croup occurring more in boys versus girls (49). The biological explanation for this is vague. We plan to investigate the sex difference in our population in a logistic regression model. In other to perform more sophisticated sex and gender analysis, we are collecting sex of patients in each treatment arm (**Figure 1**). Because evidence also supports gender difference in ED attendance (50), we will test the effect of interaction between sex and gender on return visits or readmission due to either dose of dexamethasone in regression models.

QUALITY MANAGEMENT AND INVESTIGATOR'S RESPONSIBILITIES

Clinical site monitoring will be 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 International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), Tri-Council Policy Statement 2 (TCPS2) and with applicable regulatory requirement(s), such as Health Canada.

Monitoring of data integrity, regulatory compliance and participant safety will be performed in accordance with our trial monitoring plan, which will include review of CRFs and other study documents for compliance, data accuracy and completeness. Monitoring will include monitoring visits to investigational site during the study for source data verification, review of the investigator's site file and drug handling records. The assigned monitor will be given direct access to source documents, CRFs and other study-related documents by the Qualified Site Investigator. By signing the informed consent form, the parent or guardian gives authorized assigned monitor to directly access to the participant's medical records and the study data. This study may be subject to audit or inspection by representatives of the organization contracted for monitoring or representatives of Health Canada.

Qualified Site Investigator and the institution will permit trial-related monitoring, audits, HREB review (such as the participating site's HREB, the Sponsor-Investigator Quality Assurance staff, and regulatory inspectors from Health Canada) by providing direct access to the participants original medical records for verification of clinical trial procedures and /or data, as well as essential documents, MOP (including electronic information), ethics and pharmacy documentation. As this trial will be conducted under a CTA with Health Canada, the site may be subject to an inspection by the Health Canada Inspectorate.

Noncompliance with the protocol, MOPs, GCP, and/or applicable regulatory requirement(s) by a site investigator/institution, or by a member of the Sponsor-Investigator staff will lead to prompt action by the Sponsor-Investigator to secure compliance.

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the Sponsor-Investigator will perform a root cause analysis and implement appropriate corrective and preventive actions.

If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of a site investigator/institution, the Sponsor-investigator will terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the Sponsor-Investigator will notify promptly the regulatory authorities.

The Sponsor- Investigator will be responsible for implementing and maintaining quality assurance and quality control systems with written MOPs to ensure that trials are conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. The Sponsor-Investigator will be responsible for securing agreements from all involved parties to ensure direct access to the trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by regulatory authorities.

The ultimate responsibility for the quality and integrity of the trial data will reside with the Sponsor-Investigator. Any trial related duty that is transferred to and assumed by a third party will be specified in writing. The Sponsor-Investigator will document approval of any subcontracting of trial-related duties.

DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection and entry is the responsibility of the clinical trial staff at the site under the supervision of the Qualified Site Investigator. The qualified site investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Paper records (e.g. copies of consent and assent forms) will be stored exclusively in the research office in a locked cabinet at each site.

Data management services will be provided by the George and Fay-Yee Centre for Health Care Innovation (CHI). Data will be entered into a validated electronic, web based, data capture system (REDCap) and will be managed according to approved data management and quality plans. During the data collection process data may be collected on paper and transcribed into the study database or, in some cases, information obtained directly from the participants may be entered directly into the study database. Under these circumstances the study database may be considered to be an electronic source document. Selected data elements will be validated electronically on an ongoing basis throughout the study and any discrepancies will be

assigned to members of the study team for resolution.

The study team will provide hardcopies of the study worksheets for use as source document for recording data for each participant enrolled in the study if REDCap or Internet access is unavailable. Hardcopy data will be entered into REDCap as soon as the online systems are available. Data derived from hardcopies should be consistent with the data recorded on the source documents.

Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents. Source documents contain source data from all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into REDCap. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents, participants, or study team.

PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH-GCP), or Study Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the qualified site investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH-GCP E6 (R2) on compliance with protocol, quality assurance and quality control and noncompliance. The definition of a reportable deviation generally includes an unanticipated deviation or divergence from the approved research protocols, consent document(s) or study addenda that may jeopardize participant safety, study efficacy, or data integrity.

In accordance with ICH-GCP section 4.5.3, it is the responsibility of the Qualified Site Investigator to use continuous vigilance to identify and report protocol deviations that jeopardize participant safety, study efficacy or data integrity to the Sponsor- Investigator within 15 working days of identification of the protocol deviation, or within 15 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the UoM BREB per the protocol deviation reporting policies. The Qualified Site Investigator is responsible for knowing and adhering to the responsible BREB requirements.

Key Roles and Study Governance

Sponsor- INVESTIGATOR

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Study Coordinator: Banke Oketola

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The Sponsor-Investigator will delegate a member of her research team to manage the day-to-day operations of this trial. The qualified site investigator and site coordinator will be responsible for the day-to-day operations at the site and responsible for following the protocol. The Sponsor-Investigator will be responsible for reporting on anticipated clinical outcomes to the Steering Committee. The Data Science Platform of CHI will be responsible for the data analysis and providing reports to the DSMB.

Study Committees

Data and Safety Monitoring Board (DSMB):

The safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise and shall include individuals experienced in statistics, pharmacology, and pediatric emergency medicine. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DMSB will operate under the rules of an approved charter that will be reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be defined. The DSMB will meet when the study achieves 50% enrolment (25 participants). Additional meetings may be required at the discretion of the DSMB chairman to discuss safety issues. They will receive a blinded interim report on safety but can, if necessary, ask for unblinding. They will be advised in a timely manner of any SAE or SADR and any urgent unblinding decisions. Ad hoc meetings may be called as necessary to discuss these events. The DSMB will provide its input to the Sponsor- Investigator and the Site PI and where required by regulations and guidelines to UoM HREB, and Health Canada.

Steering Committee:

This committee shall be made up of pediatric emergency physicians, trialist, and pediatric emergency medicine researchers. They will provide guidance in implementing the study. The committee will have scheduled meetings. They will be provided with the progress report of the trial in a timely manner.

Phase 2b: Determining the noninferiority margin.

The noninferiority margin is the number of revisits/readmission for croup that clinicians can tolerate when children are treated with 0.15mg/kg versus 0.60mg/kg. To determine the non-inferiority margin for dexamethasone at 0.15mg/kg, we will conduct two surveys containing case scenarios to sample ED physicians (41) (**Appendix B for details**). Implied consent will also be used for the noninferiority exercise, meaning that by agreeing to participate in the noninferiority survey, the emergency physicians agree that their data can be used for research. This will run concurrently with the vanguard RCT.

Phase 2c: The Elicitation Process (Innovation 1):

We will use the adapted Sheffield Elicitation Framework (SHELF) methodology (38-40) for the remote elicitation exercise with a web-based interactive elicitation tool. We will build using R software and the shiny package. The online tool will provide real-time individual feedback on the elicitation to ensure the elicited distributions capture the experts' beliefs. REDCap will be used to collect the elicited distributions from each expert. We will target experts from Canada, the United States, Australia and New Zealand, and Europe/United Kingdom to determine

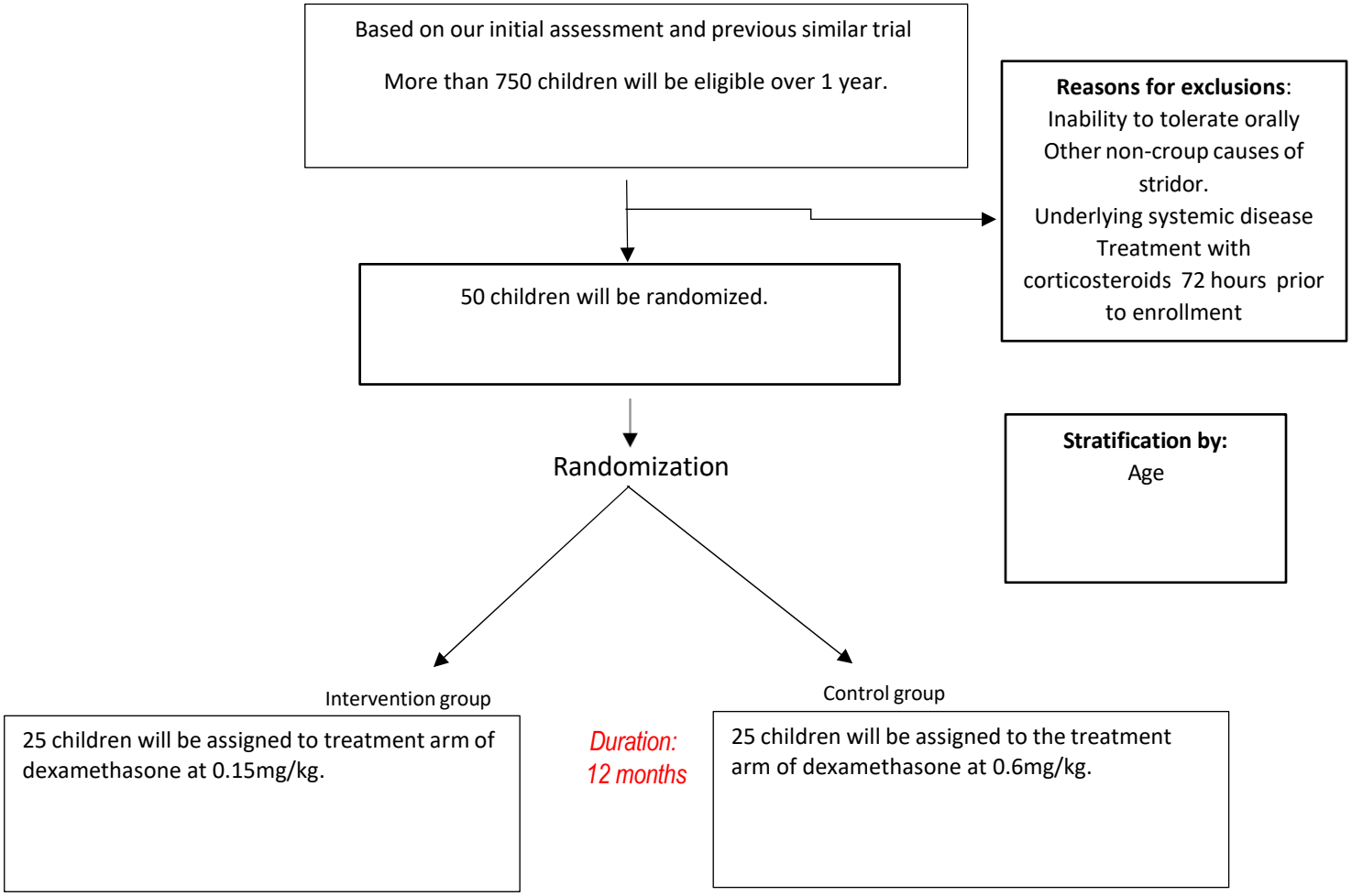
representative aggregate priors across regions and avoid selection bias. Participants will be eligible for the elicitation workshop if they (i) were identified as experts in croup and its treatment and (ii) had experience in pediatric emergency medicine. Participants will be excluded if they authored any studies that preferred dexamethasone at either 0.6mg/kg or 0.15mg/kg. Potential participants will be invited to contribute by email. We will recruit 15 experts to cover experience in terms of geography and specialty. ***The authors' exclusion criteria and the decision to recruit 15 experts was based on the methodology of a similar trial published by our team (35), which shows that this number is effective***. The elicitation will take place in two remote, real-time workshops using Zoom platform to account for differences in time zones. Implied consent will be used for the remote elicitation exercise, meaning that by agreeing to participate in the elicitation exercise, the experts agree that their data can be used for research.

Table 1. Study timeline and activities (2023-2025):

The study is divided into 3 phases that overlap.

Phase	Period	Activity
Phase 1	Year 1	**Ethics approvals** 1. Obtain approval from the Health Research Ethics Board of UM, Shared Health Manitoba and Health Canada 2. Register the trial protocol and statistical plan on clinicaltrials.gov 3. Recruit research staff and trainees 4. Create and complete consent forms, case report forms (CRFs) posters, other patient facing documents for the vanguard RCT 5. Develop CRFs in REDCap
Phase 2	Year 1	**Implementation of the vanguard RCT, Bayesian elicitation, & Noninferiority determination.** 1. Develop an online elicitation tool 2. Select the experts 3. Collect workshop materials 4. Implement a real-time expert elicitation workshop 5. REDCap development to sample physicians for the noninferiority determination 6. Survey distribution to sample physician for noninferiority determination 7. Recruit and randomize patients for the vanguard RCT 8. Commence intervention
Phase 3	Year 1 Year 2 Year 3	**Patient engagement, data analysis & preliminary results** 1. Find and engage patient partner families 2. Priorities goals from partner families to inform next steps 3. Planning next steps and how to best collect data to track patient priorities (phone / text / survey) 4. Reviewing data from vanguard with the research team 5. Support KT by distributing findings of vanguard to health care providers and families to receive feedback 6. Support the grant writing for the larger multicenter definitive RCT.

Figure 1: Recruitment and randomization of patients with diagnosis of croup



Appendices

Appendix A: ICD -10 for croup diagnosis and adverse events

Appendix B: Noninferiority Margin Survey

Appendix C: Recruitment Poster

Appendix D: Research Participant Information and Consent form

Appendix E: Master list

Appendix F: Baseline Case Report Form

Appendix G: Follow-up Case Report Form

Appendix H: Manual of Operations (MOP)

Appendix I: Pharmacy Manual

Appendix J: Product Monograph

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