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Dexamethasone versus prednisone for asthma treatment in the pediatric inpatient population; a feasibility randomized controlled trial

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Figure 1: Schematic of Study Design
Supplementary File 1: Physician Orders for Asthma in the ED order set
Supplementary File 2: Physician Orders for Asthma Respiratory Failure in the ED order set
Supplementary File 3: Emergency Department Nursing Medical Directive
Supplementary File 4: Study Order Sheet

ABSTRACT

Introduction

Asthma exacerbations are a leading cause of pediatric hospitalizations. Corticosteroids are key in the treatment of asthma exacerbations. Most current corticosteroids treatment regimens for children admitted with asthma exacerbation consist of a 5-day course of prednisone or prednisolone. However, these medications are associated with poor taste and significant vomiting, resulting in poor compliance with the treatment course. While some centers already use a short course of dexamethasone for treating children hospitalized with asthma, there is no evidence to support this practice in the inpatient population.

Methods and analysis

This single-site, pragmatic, feasibility randomized controlled trial, will determine the feasibility of a non-inferiority trial, comparing two treatment regimens for children admitted to the hospital with an acute asthma exacerbation. Children 18 months to 17 years presenting to a Canadian tertiary care centre will be randomized to receive either a short course of dexamethasone or a longer course of prednisone/prednisolone once admitted to the inpatient units. The primary clinical outcome for this feasibility study will be readmission to hospital, or repeat Emergency Department visits, or unplanned visits to primary health care providers for asthma symptoms within 4 weeks of hospital discharge. Feasibility outcomes will include recruitment and allocation success, compliance with study procedures, retention rate, and safety and tolerability of study medications. We plan on recruiting 51 children, and between-group comparisons of the clinical outcome will be conducted to gain insights on probable effect sizes

Ethics and Dissemination

Research Ethics Board approval has been obtained for this study. The results of this study will inform a multi-site trial comparing prednisone/prednisolone to dexamethasone in inpatient asthma treatment, which will have the potential to improve the delivery of asthma care, by improving compliance with a mainstay of treatment. Results will be disseminated through peer-reviewed publications, organizations and meetings.

Trial Registration:

Clinialtrials.gov: NCT03133897

Article Summary

Strengths and limitation of this study:

- This pragmatic feasibility trial paves the way for a large multi-site pragmatic trial which will compare a short course of dexamethasone to a longer course of prednisone / prednisolone in the treatment of inpatient asthma.
- As patients are enrolled after the decision to admit to hospital has been made, there is no restriction on the type of corticosteroid prescribed by the Emergency Department physician on presentation, allowing for generalizability and applicability to most pediatric clinical settings.
- Participants and health care providers will not be blinded to the intervention; this will however allow for better generalizability and interpretation of results as palatability of

prescribed corticosteroids and length of treatment are known to affect compliance, which would both be lost with blinding.

List of Abbreviations

- CS: Corticosteroids
- CHEO: Children's Hospital of Eastern Ontario
- ED: Emergency Department
- IV: Intravenous
- POS: "Physician Orders for Asthma in the ED" and "Physician Orders for Asthma Respiratory Failure in the ED" order sets
- PI: Principal Investigator
- PRAM: Pediatric Respiratory Assessment Measure
- DSMB: Data Safety Monitoring Board
- REDCap: Research Electronic Data Capture
- AE: Adverse Events
- SAE: Serious Adverse Events

INTRODUCTION

Asthma is the most common chronic disease of childhood,[1] affecting approximately 15% of children and youth in Canada.[2] Asthma continues to be one of the leading cause of hospitalization in children.[3] In Ontario, the burden of illness related to asthma is enormous, accounting for one third of government health expenditures for the general population.[4]

A key element for treating children with acute asthma exacerbations is the administration of systemic corticosteroids (CS). Systemic CS reduce the need for hospitalization and the risk of relapse after initial treatment, and may also facilitate an earlier discharge from the hospital.[5] Some centres already use a short course of dexamethasone for inpatient asthma management. However, while data is promising for outpatients, there is no evidence to support this practice in the inpatient population. Most current CS regimens for the treatment of children hospitalized with an asthma exacerbation consist of a 5-day course of prednisone or prednisolone.

There is evidence that 2 days of once daily dexamethasone is a least as effective as 5 days of prednisone for preventing relapse in outpatient pediatric asthma.[6] In addition, patients receiving dexamethasone are significantly less likely to experience vomiting in the ED and even after returning home.[6] Preliminary cost-estimates suggest that dexamethasone may save at least $3500 per 100 patients compared to traditional treatment with prednisone or prednisolone.[7]

Prednisone is only available in Canada as a tablet or compounded suspension, which limits use due to swallowing ability and accessibility. When compared to dexamethasone, prednisolone is associated with poor palatability and significant vomiting.[8] Both prednisone and prednisolone are associated with poor compliance. Prednisone and prednisolone are compounded with similar recipes, and therefore have a similar taste. Compliance with 5 days of prednisone has been

estimated in one study to be as low as 64% for pediatric asthma. [9] As determined by a systematic review conducted by the principal investigator (PI) of this current study (PROSPERO 2016:CRD42016041766), studies comparing dexamethasone to prednisone in hospitalized patients are lacking. Promisingly, a retrospective cohort study in pediatric inpatients hospitalized with asthma suggested that dexamethasone, when compared to prednisone/prednisolone, may result in a shorter length of hospital stay and reduced costs with no difference in number of transfers to intensive care or readmissions.[10]

Dexamethasone is a potent glucocorticoid with a long half-life, therefore concerns have been raised regarding its potential for adrenal suppression. However, a study of high-dose (~1.7 mg/kg) dexamethasone in acute asthma found no significant difference in adrenal function between single-dose dexamethasone and 5 days of oral prednisone at day 14.[11]

Given the importance of CS in the treatment of asthma, the significant decrease in relapse risk associated with their use, and the high prevalence of childhood asthma, there is a need to determine whether a better tolerated and more convenient CS can be used as first line therapy. Although outpatient data on this issue exists, extrapolating treatment regimens from the outpatient population may not be appropriate as hospitalized children represent a sicker group of patients than those discharged from the emergency department.
In order to determine whether dexamethasone is at least as effective as prednisone/prednisolone in the treatment of inpatient asthma, we propose a feasibility study, as a first step in the development of a future multi-site trial.
Specifically, we plan to determine the feasibility of a non-inferiority trial, comparing a short course of dexamethasone to the more traditional longer course of prednisone/prednisolone for inpatient asthma treatment. We will determine the feasibility of:

1- Enrolling patients upon admission to hospital, after they receive their first dose(s) of CS in the ED
2- Asking patients and/or caregivers to complete a symptom diary weekly for 4 weeks
3- Reassessing patients 7 days after hospital admission day
4- Successfully completing phone follow up 4 weeks post-hospital discharge
5- Collecting health utilization data post-hospital discharge.

METHODS AND ANALYSIS

Trial design

This trial will be conducted at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario, Canada. Children with asthma, admitted from the emergency department (ED) to the clinical teaching units will be eligible for the study (see Figure 1 for schematic of study design). Trial recruitment commenced in February 2018. This protocol follows SPIRIT guidelines.

A pragmatic design[12] was chosen to strengthen the generalizability of our findings, as the effectiveness of the intervention is being tested across routine clinical practice. Blinding of the participants and members of the health care team will not be undertaken in this study. Since the palatability of the CS is likely to affect compliance, masking the taste of the CS similar to ensure blinding would decrease ability to detect a difference in compliance due to taste. Moreover,

given the length of therapy for prednisone/prednisolone is longer than that of dexamethasone, introducing placebo doses to ensure similar length of treatment would also potentially impact compliance and undermine the ability to detect a difference between groups. Investigators, data analysts, and research assistant completing patient assessment at the follow-up visit will however be blinded to group assignment.

Eligibility Criteria

Inclusion Criteria

Participants must meet all of the inclusion criteria listed below to participate in the study:

- Children admitted during the study period who are receiving asthma treatment for acute respiratory exacerbation as determined by the admitting physician and/or his/her representative
- Children aged 18 months to 17 years of age
- Children who have received oral or intravenous (IV) CS in the ED prior to admission under the institution's "Physician Orders for Asthma in the ED" and "Physician Orders for Asthma Respiratory Failure in the ED" order sets (POS) or "Emergency Department Nursing Medical Directive" (see Supplementary Files 1, 2 and 3 respectively)
- Children who have received IV CS for a total duration ≤ 24 hours since first dose of steroid administration in ED
- Participants must be capable of giving informed consent or have an acceptable surrogate capable of giving consent on their behalf

Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation

- Children who received oral or IV CS in the ED prescribed in any other way than the institution's POS or Nursing Medical Directive as doses may not be standardized
- Children who have received more than one dose of oral CS prior to enrolment
- Children who received oral or IV CS in the previous 2 weeks
- Children with any of the following: unrepaired congenital heart disease, cardiac disorder, chronic lung diseases other than asthma, such as bronchopulmonary dysplasia or cystic fibrosis, neurological or neuromuscular disease, sickle cell disease
- Children presenting with stridor
- Children admitted to the Pediatric Intensive Care Unit
- Children whose caregivers do not understand English or French

Intervention

Study Medication Description – Dexamethasone

Children randomized to the dexamethasone group will receive the approximate pharmacologic equivalent of two doses (days) of dexamethasone 0.6 mg/kg/dose (maximum dose 16 mg per dose) as current evidence supports the use of this dose for the inpatient population.[10,13]

The standard dose of dexamethasone provided in the ED is 0.3 mg/kg, while the standard dose of prednisone/prednisolone is 2 mg/kg (maximum single dose 50 mg), which is approximately

equivalent to 0.3 mg/kg of dexamethasone.[14] Once enrolled, children who received dexamethasone 0.3 mg/kg or prednisone 2 mg/kg in the ED will be administered a "top-up" dose of dexamethasone at 0.3 mg/kg (maximum dose 8 mg). They will then receive a dose of dexamethasone 0.6 mg/kg (maximum dose 16 mg) 24 +/- 6 hours after the initial CS dose received in the ED (see Supplementary File 4 for Study Order Sheet). The dexamethasone dose will be rounded to the nearest 0.25 mg upon initial prescribing. Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purposes of the pharmacist rounding to available dosage forms.
Children who have received IV methylprednisolone in the ED and who are randomized to the dexamethasone group will not receive a top-up dose upon study enrolment. They will receive one dose (day) of dexamethasone 0.6 mg/kg/dose (maximum dose 16 mg per dose) 24 hours after the initial dose of oral CS in the ED and at least 6 hours after the last dose of IV methylprednisolone (see Supplementary File 4 for Study Order Sheet).

Standard of Care Description- Prednisone / Prednisolone
Children randomized to the prednisone / prednisolone group will receive four doses (days) of prednisone / prednisolone 1 mg/kg/dose once daily (maximum single dose 50 mg) following the initial dose of CS received in the ED (see Supplementary File 4 for Study Order Sheet).The prednisone dose will be rounded to the nearest 0.5 mg upon initial prescribing. Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purposes of the pharmacist rounding to available dosage forms.

Children who have received IV methylprednisolone in the ED and are randomized to the prednisone / prednisolone group will receive four doses (days) of prednisone / prednisolone 1 mg/kg/dose daily (maximum dose 50 mg). Study medication will be given 24 hours after the initial dose of oral CS in the ED and at least 6 hours after the last dose of IV methylprednisolone (see Supplementary File 4 for Study Order Sheet).

Children in both groups will receive asthma standard of care as dictated by their treating health care team, in addition to the study drug.

Study outcomes
Primary clinical outcome for feasibility study
(1) Readmission to hospital for asthma, repeat ED visit within 4 weeks for asthma, or unplanned visits to primary health care providers for asthma symptoms.

Feasibility Outcomes
(1) Allocation success; proportion receiving assigned CS as per randomization group
(2) Recruitment success; number screened, number eligible, number enrolled
(3) Compliance with reporting symptoms in diary
(4) Retention rate: a) Proportion of patients coming back for follow-up visits; b) Proportion of patients reached at 4-week follow-up
(5) Safety of each CS
(6) Tolerability of each CS

Clinical outcomes for multicenter study:

The primary outcome for the multicenter study will be finalized following the feasibility study. As such, clinically relevant outcomes that will be measured in this feasibility study include:

(1) Readmission to hospital for asthma within 4 weeks of ED presentation determined using parent report, and CHEO chart review
(2) Repeat ED visits for asthma symptoms within 4 weeks of ED presentation determined using parent report, and CHEO chart review
(3) Unplanned visits to physicians / nurse practitioners for asthma symptoms measured by parent report, and CHEO chart review
(4) Pediatric Respiratory Assessment Measure (PRAM) as measured on day 7 by a research nurse or study team physician. The PRAM score is a validated and reliable tool used to determine asthma severity in children.[15] Using PRAM score, rather than symptom recurrence, is more precise as a measure of symptom severity and has been used in a recent outpatient pediatric asthma RCT comparing dexamethasone and prednisolone.[16]
Health utilization data (readmissions, ED visits, unplanned visits to family physicians) will be determined through phone recall and health records.
(5) Number of children completing assigned CS treatment
(6) Asthma symptom frequency as measured by diary
(7) Length of hospital stay in hours
(8) Vomiting associated with CS administration as determined by parental interview and medical record review

Enrollment and Screening

A research assistant will review the list of admissions for the previous 12 hours, on a twice daily basis, from Monday to Friday. The research assistant will then ask a member of the patient's health care team (bedside nurse, charge nurse, resident, staff physician) to ask the family members for permission to approach the family about the study. The research assistant will then complete a screening log and maintain a phone follow-up ledger for consented patients. If the patient is eligible and the family gives their informed consent, and the child their assent if appropriate, they will be allocated to one of the study groups. Once written, informed consent has been obtained, the research assistant will communicate with the health care team to ensure the patient continues on the CS he/she has been randomized to, for the appropriate number of doses as determined by CS group assignment. A record will be kept of all screened patients, patient eligibility, allocation, and follow up to allow reporting according to CONSORT guidelines.[17]

Randomization and baseline visit (hospitalization)

After enrollment, the patients will be randomly allocated to one of the two treatment groups (day 0). The randomization schedule will have been previously generated using a computer. Randomization will be blocked with randomly chosen block lengths of 4 or 6. Treatment assignments will be written on a piece of paper and concealed in sequentially numbered opaque envelopes kept in a secure locked location in the study research office. The PI and analyst will be blinded to the treatment intervention, but the research assistant in charge of screening and randomizing patients, as well as the patient's treating team (physicians and nurses) will not because of the pragmatic nature of the trial. Demographic data will be collected at baseline.

Follow up visit

Patients will be reassessed 7 days after admission day to hospital, +/- 3 days to allow for flexibility with patient's schedule, weekends, holidays and unexpected events. Patients will receive a physical examination by a study physician, and an assessment of asthma symptom severity through the PRAM score[15]. At that visit, we will collect compliance data with both courses of treatment, and remind participants to begin charting asthma symptoms in their symptom diary. PRAM scores at the follow up visit will be collected on the case report form. Data on Adverse Events (AE) and Serious Adverse Events (SAE) will also be collected at that visit. Patients unable to come back for the day 7 visit will receive a phone call from a study physician to ensure the family has no concerns. If the participant consents, a partial PRAM assessment will be done via video conference call by the study physician.

Phone follow up

Phone follow up will be performed at 4 weeks post-hospital discharge, +/- 7 days to allow for flexibility with patient's schedule, weekends, holidays and unexpected events. Data on return visits to health care providers, ED visits and hospital readmissions will be collected by phone 4 weeks post-hospital discharge, as well as data on AE and SAE.

Data on patients' experience with prescribed CS will also be collected at the follow up phone call via semi-structured phone interviews.

Expected duration of participant participation

Study subjects are expected to participate in the study from enrollment until 4 weeks after hospital discharge (see Figure 1)

Parents and/or caregivers in both study groups will be asked to electronically complete a standardized validated symptom diary weekly, starting 7 days post discharge until 4 weeks post discharge (The Asthma Quiz for Kidz). Patients who prefer a paper copy of the questionnaire will be provided with 4 questionnaires prior to hospital discharge, as well as preaddressed stamped envelopes to facilitate mailing back of the questionnaire. The Asthma Quiz for Kidz is a short 6-item questionnaire validated for in French and English for children aged 1 to 17 years.

Formulation, Packaging and Labelling

Dexamethasone

Patients will receive dexamethasone orally as tablet(s) or compounded suspension based on patient or health care provider preference. The dexamethasone suspension will be compounded at the CHEO research pharmacy using a combination of dexamethasone sodium phosphate USP injection 10mg/mL (^{PR}Dexamethasone Omega Unidose; see product monograph) manufactured by Omega Laboratories Ltd. and Ora-Blend®, a flavored oral suspending vehicle manufactured by Galenova Inc. The compound is created by combining 10mL of the dexamethasone 10mg/mL sodium phosphate USP and 90mL of Ora-Blend®. The final oral suspension has a concentration of 1mg/mL of dexamethasone and a pinkish hue with a milky consistency. The appropriate dose for the participant will be drawn up into an oral syringe, which will be labeled for investigational use.

Prednisone / Prednisolone

Patients will receive prednisone/prednisolone orally as tablet(s) or compounded suspension (prednisone) or as a commercially available liquid (prednisolone). The prednisone suspension will be compounded at the CHEO research pharmacy using a combination of APO-prednisone

50 mg tablets ([PR]APO-PREDNISONE 50 mg tablet; see product monograph) and Syrup, NF (Simple) a sweetened vehicle manufactured by Medisca at a ratio of one 50 mg tablet for every 10 mL of Syrup, NF (Simple). The final oral liquid has a concentration of 5 mg/mL with a yellow to white hue and clear to milky consistency. The appropriate dose for the participant will be drawn up into an oral syringe, which will be labeled for investigational use.

Sample Size Determination

We sought a sample size that would allow us to estimate our feasibility outcomes with reasonable precision. As such, we have set out to achieve a 15% margin of error (i.e. half-width of 95% confidence interval=0.15) for any proportions to be estimated (e.g. allocation success, retention success). At a hypothesized proportion of 50%, we determined that 43 patients will be needed to achieve this level of precision. This provides a most conservative estimate since any proportions other than 50% will require fewer patients. Factoring in an additional 15% of patients as allowance for attrition or incomplete data we will set a recruitment target of n=51 in total. With approximately 18 asthma admissions per month, assuming 70% are eligible and 50% of eligible patients consent, we expect to meet this sample size requirement in 9 months.

Quantitative Data Analysis

For all relevant feasibility outcomes, binary proportions (e.g. % success) and the associated 95% confidence interval will be estimated using the Wilson method. To help inform the design of main trial (i.e. expected effect sizes), we will apply intention-to-treat principles and estimate the treatment effect (and 95% CI) by comparing outcomes (proposed for the main trial) between intervention groups using statistical techniques appropriate to the type and distribution of the various outcomes (e.g. continuous, binary, count data).

Qualitative Data Analysis

Semi-structured interviews at week 4 will be audio taped and transcribed verbatim. Analyses will be conducted using Nvivo 9 software. Inductive analysis will be used to identify categories, patterns and themes.[18]

Role of the Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be set up for this study. An initial meeting will occur prior to enrolling the first patient to determine the terms of reference, review Health Canada-mandated SAE reporting and safety outcomes. Given that this trial is a feasibility trial as opposed to an efficacy trial, no interim analysis for efficacy will be performed. The DSMB will meet every 4 months after the initial meeting, until study completion. Study results will be analyzed after all participants have completed the study.

SAFETY AND ADVERSE EVENTS

Patient safety will be ensured by using standard pediatric dosing[10,13], by adhering to the inclusion and exclusion criteria, and by following the current standard of care for mitigation of treatment side effects. Patients whose PRAM scores are greater than 1 on follow up visits will be treated appropriately. A follow-up with a study physician will be booked if necessary. The patient's family physician will also be contacted to ensure appropriate follow up. The patient's

family will be instructed to come to the ED immediately in the case of symptom worsening, and to page the study physician who assessed the patient. Patients whose PRAM scores are greater than 3 on follow up visits will be immediately sent to the CHEO ED.
Patients unable to come back for the day 7 visit will receive a phone call from a member of the study team to ensure the family has no concerns. If health concerns are identified, patients will be asked to come to CHEO to be assessed by a member of the study team. If the family refuses, patients will be encouraged to visit the closest ED or to visit their family physician. A member of the investigative team will also call the family physician's office to ensure the patient is seen promptly.

MONITORING

The investigator will ensure the trial is adequately monitored in accordance to the protocol and applicable regulatory requirements. An internal monitoring visit will be completed by the CHEO Research Institute Quality Assurance (QA) team after the first participant is enrolled and further monitoring by the Quality Assurance team can be requested by the investigator, if required. Peer review, on-site monitoring visits will be completed by an investigator-appointed monitor who is familiar with the study medication and protocol. The monitor will ensure that the trial is conducted and documented according to Good Clinical Practices. As a Health Canada regulated trial, this study may be inspected at any time by Health Canada.

DATA HANDLING AND RECORD KEEPING

Data Management Responsibilities

Information will be collected for each participant by a member of the research study team at each point of study data collection. Participants will be assigned a randomization code at baseline and their records will be identified using this code so that all study subjects are non-identifiable by their study documents.

The PI and research assistant will be responsible for the overall supervision of the study. The research assistant will be responsible for recruiting patients, communicating with the nursing staff to ensure patients receive the right CS after the initial dose received in the ED, supervising the chart review and conducting the phone follow ups. Study team physicians will be responsible for patient reassessment 7 days after initial presentation.

Subject data will be recorded on source documents and transferred to REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) 128 bit encryption between the data entry client and the server (https); 3) audit trails for tracking data manipulation and export procedures; 4) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 5) procedures for importing data from external sources; and 6) advanced features, such as branching logic and calculated fields.
REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at CHEO. The application and data are housed on servers

provided by CHEO. These servers are located within CHEO's secure data centre. The data centre is physically secured through limited badge access and security cameras. Local support for REDCap is provided by CHEO's Clinical Research Unit.

Confidentiality

All participant related information including Case Report Forms, laboratory specimens, reports etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Participants will be identified only by means of a coded number specific to each participant. All computerized databases will identify participants by numeric codes only and will be password protected or encrypted.

Upon request, participant records will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of a participating pharmaceutical sponsor and applicable regulatory agencies such as Health Canada or The Food and Drug Agency.

Record Retention

All research records will be retained for 25 years after closure as required by Health Canada. All study documentation will be kept in a secure location at the study site.

Data Safety Monitoring Board (DSMB)

This study will be monitored by an independent DSMB, consisting of an independent physician, and two other members not involved in this study. The DSMB will be immediately informed of any serious SAE which may potentially be study drug related. Other SAEs will be reviewed during regular DSMB meetings. Interim reports, prepared by the data management team for the study, for review by the DSMB will include data on recruitment, compliance, adverse effects, baseline comparability and treatment comparisons. An agreed upon blinded review package which contains the appropriate data summary by treatment will be provided by the study statistician for the purposes of these reviews. The review package could then be unblinded at the request of the DMSB.

Patient and public involvement

Patients and the public were not directly involved in the design of the study. The intervention was chosen on the basis of studies reporting poor compliance with current CS used in the treatment of inpatient asthma [9] due to poor palatability of the drug and associated vomiting.[8] Study results will be disseminated through patients and study participants through our institution's social media platform.

Ethical Considerations

This study will be conducted in full conformance with the principles of the 'Declaration of Helsinki', GCP and within the laws and regulations of Canada (Health Canada, Food and Drug Act, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects).

Protocol and amendments will be submitted to the CHEO REB for formal approval to conduct the study. The decision of the REB concerning the conduct of the study will be made in writing to the investigator.

All participants for this study will be provided a consent form and assent form if applicable, describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. These consent and assent forms were submitted with the protocol for review and approval by the REB. The formal consent of a participant, using the REB-approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form must be signed by the participant or legally acceptable surrogate and the investigator-designated research professional obtaining the consent. Patients will be free to withdraw from study participation at any point in time and will receive the same standard of medical care given to all patients admitted with asthma to the pediatric ward at CHEO. The data collected during this trial will be held confidential.

All study investigators will have access to the final trial dataset. The International Committee of Medical Journal Editors authorship eligibility guidelines will be used for publication. We plan on disseminating our study results through peer reviewed publications, professional organizations and conferences.

Author Contributions

Catherine Pound conceived and designed the study and drafted the first version of the manuscript, and approved the final version of the manuscript.
Jaime McDonald participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Ken Tang participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Gillian Seidman participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Radha Jetty participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Sarah Zaidi participated in revising the study protocol, read and reviewed the manuscript and approved the final version of the manuscript.
Amy Plint participated in and supervised the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.

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Competing Interests:

None of the authors have any competing interests to disclose

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decision to submit this manuscript for publication, and will have no authority over management, analysis and interpretation of data.

Data sharing

Data collection forms can be requested through the corresponding author.

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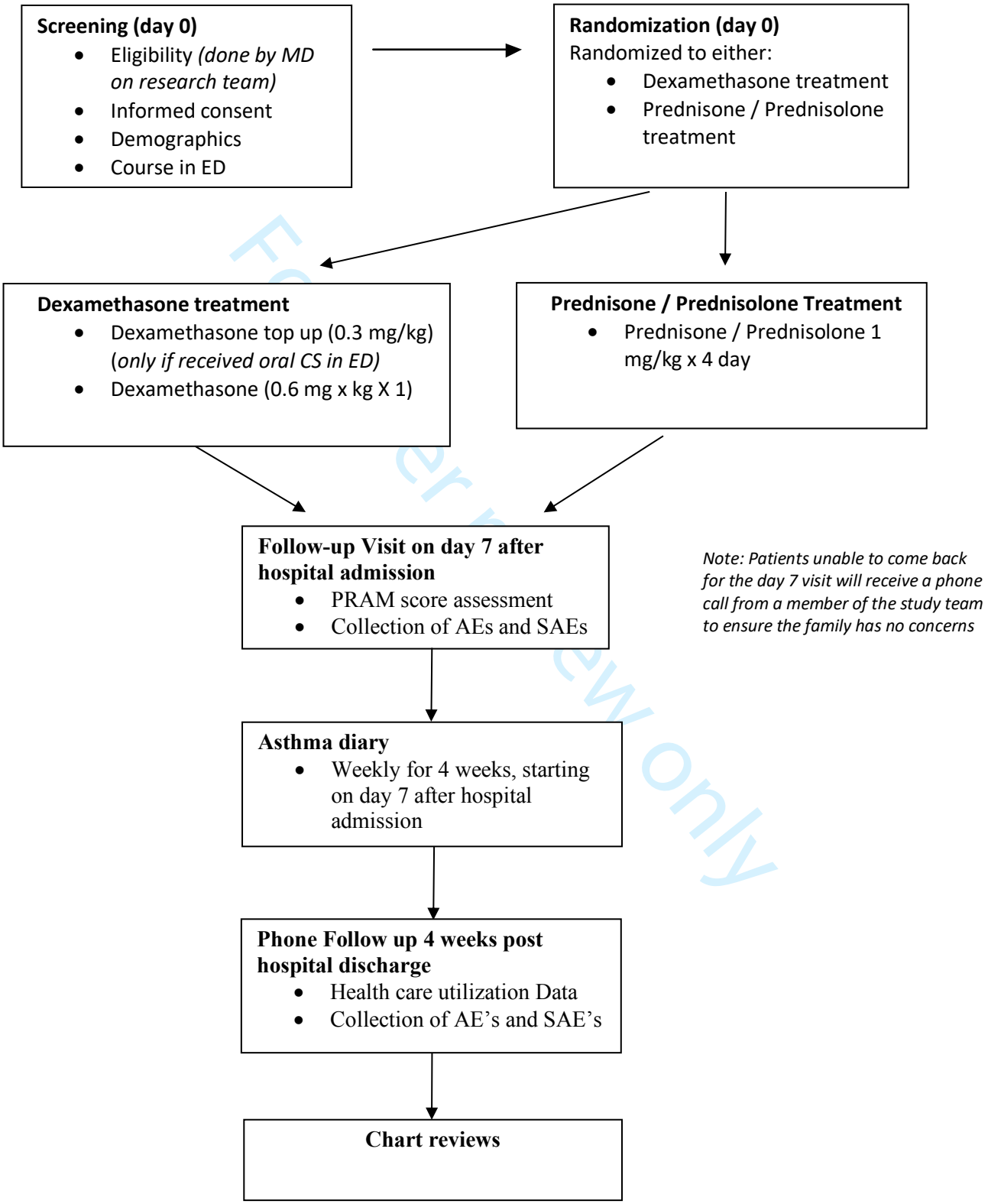
Figure 1
Schematic of Study Design



Physician Orders for Asthma in the ED [250]

For severe respiratory distress/signs of respiratory failure OR Failure to improve after 1 hour of treatment select Order Set # 251 Asthma - Severe Respiratory Distress/Failure to Improve after initial treatment.

General

CHEO NURSING INTERVENTION PRE SEND PATIENT WITH MED

☑ Send Patient home with Medications	Until discontinued, Starting today Unused portion of the Salbutamol MDI may be dispensed to the patient upon discharge

CHEO NURSING ASSESSMENT PRE ASTHMA PATHWAY

☐ Pathway Initiation	Until discontinued, Starting today Pathway: Asthma

Respiratory

CHEO RESPIRATORY INTERVENTIONS PRE O2 92% NO COMMENTS

☐ Oxygen Therapy	Until discontinued, Starting today SpO2 Target (equal to or greater than): 92%

Medications

For PRAM (Pediatric Respiratory Assessment Measure) Score of 1 - 3 (mild)

☐ Salbutamol MDI — **"And" Linked Panel**

☐ salbutamol 100 mcg/puff MDI PRN DOSE	Inhalation, Every 30 minutes PRN, Starting H+3 Hours PRN FREQUENCY. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

For PRAM Score of 4-7 (moderate)

☐ Salbutamol MDI 100 mcg/puff

☐ salbutamol 100 mcg/puff MDI - Select ONLY if not already ordered as per medical directive	Inhalation, Every 20 minutes, For 3 Doses (If not already given as per medical directive) Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.
☐ salbutamol 100 mcg/puff MDI PRN DOSE	Inhalation, Every 30 minutes PRN Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.

For PRAM score of 8-12 (severe)

☐ Salbutamol/Ipratroprium Nebules - Select ONLY if not already ordered under medical directive

Select ONLY if not already ordered under medical directive.

☐ salbutamol inhalation solution	Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ ipratropium 250 mcg/2 mL inhalation solution	250 mcg, Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.

☐ Salbutamol Nebules/MDI **"Or" Linked Panel**

After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI

☐ salbutamol inhalation solution	Nebulization, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ salbutamol 100 mcg/puff MDI	Inhalation, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

Physician Orders for Asthma Respiratory Failure in the ED [251]

For severe respiratory distress/signs of respiratory failure OR failure to improve after 1 hour of treatment from Order Set 250 - Asthma

General

CHEO NURSING ASSESSMENT PRE ASTHMA PATHWAY

☐ Pathway Initiation	Until discontinued, Starting today Pathway: Asthma

CHEO VITAL SIGNS PRE ASTHMA ED

☑ Blood pressure	Every 5 min During magnesium infusion
☑ Cardio Respiratory Monitor with Oxygen Saturation	Continuous

Respiratory

CHEO RESPIRATORY INTERVENTIONS PRE O2 95% NO COMMENTS

☑ Oxygen Therapy	Until discontinued, Starting today SpO2 Target (equal to or greater than): > 95%

Labs

CHEO BLOOD PRE ED ASTHMA

☑ CBC and Differential	Once
☑ Electrolytes (Whole Blood)	Once
☑ Blood Gas Capillary	Once

IV fluids

IV FLUIDS

☐ 0.9% NaCl bolus	Intravenous, Once, For 1 Doses
☐ D5-0.9% NaCl IV solution	Intravenous, Continuous

Medications

For PRAM score of 8-12 (severe)

☐ Salbutamol/Ipratroprium Nebules - Select ONLY if not already ordered under medical directive

Select ONLY if not already ordered under medical directive.

☐ salbutamol inhalation solution	Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ ipratropium 250 mcg/2 mL inhalation solution	250 mcg, Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
☐ Salbutamol Nebules/MDI	**"Or" Linked Panel**
After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI	
☐ salbutamol inhalation solution	Nebulization, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ salbutamol 100 mcg/puff MDI	Inhalation, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.
Other Medications	
☐ methylPREDNISolone (PF) 62.5 mg/mL injection	1 mg/kg/dose, Intravenous, Once, For 1 Doses Usual dose 1 - 2 mg/kg/dose, MAX 125 mg. If prednisoLONE or prednisONE already given as per medical directive, limit methylPRENISolone dose to 1 mg/kg/dose, MAX 125 mg.
☐ magnesium sulfate in 0.9% NaCl 40 mg/mL injection	50 mg/kg/dose, Intravenous, Once, For 1 Doses Usual dose: 50 mg/kg/dose, MAX 2000 mg. Give IV over 20 - 30 minutes.

CHILDREN'S HOSPITAL OF EASTERN ONTARIO

1. **Name of the Medical Directive:** Initial oral steroid for known asthmatic patients with moderate to severe respiratory distress in the Emergency Department

Approval Status (Dates)

Version/Revision	MDC Submission	MDC Approval
Version 1	Nov 30, 2009	Dec 11, 2009
Version 2	Aug 1, 2010	Aug 10, 2010
Version 2.1	Nov 9, 2012	
Version 3	July 14, 2014	October 22, 2014
Version 4	November 2017	

Effective Date: December 11, 2017 **Directive Number: 2022**
Renewal Frequency: ☐ 3 years ☑ Other (may not exceed 3 years):
Expiry Date: March 31, 2018

2. **Contact Information**
Area of Practice: Emergency Department
Medical Director: Medical Director, Emergency Department **Extension:** 2899
Developed By: Dr. Roger Zemek **Extension:** 2318

3. **Purpose Statement**
This medical directive allows nurses (RN) or respiratory therapists (RRT) to initiate and administer an oral steroid dose to Emergency Department (ED) patients with a history of asthma presenting with moderate to severe asthma exacerbations. Oral corticosteroids are the gold standard treatment in children and adults presenting with moderate to severe asthma to the emergency department, reducing by 25% the risk of hospital admission when administered within an hour of triage. This will allow the initiation of therapy for patients with moderate to severe asthma exacerbations prior to assessment by the physician. Choice of medication will be determined by whether the patient can swallow tablets (prednisone) or needs a liquid suspension (dexamethasone, prednisolone, prednisone – determined by medication availability). Dosage of medication will be dictated by the patient's weight. Patient eligibility will be determined by the patient's Pediatric Respiratory Assessment Measure (PRAM) score upon arrival to the ED.

4. **Personnel Authorized to Implement the Medical Directive**
- All staff, following appropriate orientation, must demonstrate the knowledge, skill and judgement required to apply the medical directive
  - RN hired in the ED
  - RN on the Float Team who have received training/orientation and are working in the ED
  - RRT working in the ED

5. **Patient Population and Indications**
- Alert and oriented
- Aged 1 to 17 years
- History of asthma with the use of bronchodilator(s) for prior exacerbations
- Triage PRAM (Pediatric Respiratory Assessment Measure) score of 4 to 11.

6. **Contraindications**
- PRAM score < 4
- CTAS (Canadian Triage and Acuity Score) 1 or PRAM = 12
- Any use of oral corticosteroid in the past 14 days – **DISCUSS WITH MD FIRST**
- Three prior courses of oral steroids in the past year – **DISCUSS WITH MD FIRST**
- Hypersensitivity to prednisone, prednisolone, dexamethasone or oral corticosteroids
- Patients meeting any exclusion criteria from the asthma critical pathway
- Patients with respiratory condition such as bronchopulmonary dysplasia and cystic fibrosis
- Patients with cardiac, metabolic, immunological disease, or history of adrenal suppression
- Patients with co-existing acute illness such as pneumonia, pertussis, or croup
- Exposure to varicella in the previous 3 weeks in a susceptible child.

7. Description of the Procedure

a) Identify ED patients with breathing difficulty and a history of asthma, as per the Asthma critical pathway inclusion/exclusion criteria

b) Complete a respiratory assessment using PRAM (see below) and baseline vital signs, and document within the appropriate sections of the patients health record.

c) Weigh the patient and document

d) Determine the appropriate CTAS and treatment regimen based on the patient's PRAM

- ❑ PRAM score 1 – 3: patient will be managed per the initial bronchodilator medical directive only
- ❑ PRAM score 4 – 11: patient will be managed per the initial bronchodilator medical directive and receive one dose of oral steroid, as per the dosing in the table below. This will be given as prednisone tablets, dexamethasone elixir, elixir, prednisolone suspension, or prednisone suspension (depending on drug availability) immediately following the first bronchodilator treatment and before the second dose of the initial three back to back bronchodilator treatments. (Specifically, the patient will receive the 1st inhaled treatment, then oral psteroid, then the 2nd inhaled treatment, and then their 3rd inhaled treatment).
- ❑ PRAM score 12: notify physician immediately for consideration of IV corticosteroid

e) **Any questions regarding the appropriateness or dosage of prednisone/prednisolone/ dexamethasone should be discussed with the physician prior to administration.**

f) **When an RN and RRT are working together to provide care for the patient, they must verbally communicate the assessment, plan and medications administered with each other, in addition to documenting within the electronic medication administration record (eMAR).**

g) **If at any time the patient no longer responds appropriately to treatment or deteriorates, immediately notify the physician.**

PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM)

	0	1	2	3
Suprasternal Indrawing	absent		present	
Scalene retractions	absent		present	
Wheezing	absent	expiratory	inspiratory and expiratory	Audible without stethoscope/ absent with no air entry
Air entry	normal	decreased at bases	widespread decrease	absent/ minimal
Oxygen saturation	≥ 95%	92%-94%	< 92%	

Severity Classification	PRAM Clinical Score
Mild	1 – 3
Moderate	4 – 7
Severe	8 – 12
Impending Respiratory Failure	12 plus following lethargy, cyanosis, decreasing respiratory effort, and/or rising $pC0_2$

MEDICATION DOSAGES

Prednisone Oral 5 or 50mg Tablets
2 mg / kg to a maximum of 50 mg (round up to the nearest 5 mg)
Dexamethasone Oral Elixir (1st choice if available) (1 mg / 1 ml)
0.3 mg / kg to a maximum of 10 mg (round up to the nearest 1 mg)
Prednisolone Oral Suspension (2nd choice if available) (1 mg / 1 ml)
2 mg / kg to a maximum of 50 mg (round up to the nearest 1 mg)

Prednisone Oral Suspension (last choice) (5 mg / 1 ml)
2 mg / kg to a maximum of 50 mg (round up to the nearest 1 mg)

8. Consent and Documentation

- Verbal consent will be obtained from the patient/parent prior to administration of the medication. Any refusal of treatment will be documented. Documentation of the medication, indicating "as per medical directive #2022", will be made in the patient's health record, as appropriate

9. Quality Management Process

- All RNs and RRTs will be educated about the purpose, indications and contraindications, and possible complications for administration of oral prednisone/prednisolone/dexamethasone by the clinical educator or delegate.
- All safety reports related to the administration of oral prednisone/prednisolone under this medical directive will be reviewed by the clinical manager, director and medical director. A copy will be forwarded to the Chair of the Medical Directives Committee.
- Prior to renewal of this medical directive, audits will be conducted to verify that the medical directive is being used appropriately.

10. References and Resources

- CHEO:
  - Medical Directives Policy
  - Medical Directive # 2017 – Initial bronchodilator therapy for known asthmatic patients in the Emergency Department
- College of Nurses of Ontario (CNO):
  - Practice Guidelines:
    - Authorizing Mechanisms (rev. November 2013)
    - Consent (rev. June 2009)
    - Directives (rev. November 2011)
  - Practice Standards:
    - Decisions About Procedures and Authority, Revised 2013
    - Documentation, Revised 2008 (rev. June 2009)
    - Medication, Revised 2014
    - Professional Standards, Revised 2002 (rev. June 2009)
  - The Regulated Health Professions Act (RHPA): Scope of Practice, Controlled Acts Model (2011)
- College of Physicians and Surgeons of Ontario: Delegation of Controlled Acts 2012
- College of Respiratory Therapists of Ontario: Position Statement – Medical Directives and the Ordering of Controlled Acts, September 2012.
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Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'Est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol: June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to predniSONE/prednisoLONE:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

_____ **predniSONE** or **prednisoLONE** _____ mg (1 mg/kg/dose; MAX 50 mg**; Dose to be rounded to the nearest 0.5 mg upon initial prescribing**) PO daily x 4 days starting 24 hours after first dose in Emergency Department (ED), and at least 6 hours after dose of IV steroids in ED.

For Pharmacy Use Only – Dispense:

- □ predniSONE 1 mg tablet
- □ predniSONE 5 mg tablet
- □ prednisone 50 mg tablet
- □ predniSONE 5 mg/mL oral suspension
- □ prednisoLONE 1 mg/mL oral solution

PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

□ Original Copy – Chart □ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to dexamethasone:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

TOP UP DOSE ***(for patients receiving prednisone/prednisolone OR dexamethasone in ED to a target of 0.6 mg/kg TOTAL dexamethasone or equivalent)***

NOTE: Please verify steroid and mg/kg dose in EPIC before ordering. If patient received dexamethasone 0.6 mg/kg/dose (OR more than 16 mg) in ED or IV steroids, **DO NOT GIVE TOP UP DOSE**. Standard doses according to the ED Medical Directive are 0.3 mg/kg/dose of dexamethasone (MAX 10 mg) and 2 mg/kg/prednisone/prednisolone (MAX 50 mg).

IF RECEIVED DEXAMETHASONE IN ED:

Dose: _____ mg ÷ _____ kg (pt weight) = _____ (A) mg/kg/dose

□ Top-up dose **NOT REQUIRED** (received 0.6 mg/kg/dose OR greater or equal to 16 mg in ED)

□ Top-up dose **REQUIRED** (_____ mg (0.6 mg/kg/dose) - _____ (A) mg/kg/dose = _____ (B) mg/kg/dose)

_____ **Dexamethasone** ____ mg (_____ (B) mg/kg/dose; MAX 16 mg/dose **INCLUDING** dose received in ED; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 STAT upon randomization

THEN

_____ **Dexamethasone** ____ mg (0.6 mg/kg/dose; MAX 16 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 dose 24 hours after first dose of **steroid** in ED

For Pharmacy Use Only – Dispense:

□ dexamethasone 0.5 mg tablet

□ dexamethasone 4 mg tablet

□ dexamethasone 1 mg/mL oral suspension

_____	_____	_____
PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

□ Original Copy – Chart □ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to dexamethasone:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

TOP UP DOSE ***(for patients receiving prednisone/prednisolone OR dexamethasone in ED to a target of 0.6 mg/kg TOTAL dexamethasone or equivalent)***

Patient who received IV steroids in ED do not qualify for top up dose.

NOTE: Please verify steroid and mg/kg dose in EPIC before ordering. Standard doses according to the ED Medical Directive are 0.3 mg/kg/dose of dexamethasone (MAX 10 mg) and 2 mg/kg/prednisone/prednisolone (MAX 50 mg).

IF RECEIVED PREDNISONE/PREDNISOLONE IN ED:

_____ **Dexamethasone** ____ mg (0.3 mg/kg/dose; MAX 8 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 STAT upon randomization

THEN

_____ **Dexamethasone** ____ mg (0.6 mg/kg/dose; MAX 16 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 dose 24 hours after first dose of **steroid** in ED

For Pharmacy Use Only – Dispense:

- ☐ dexamethasone 0.5 mg tablet
- ☐ dexamethasone 4 mg tablet
- ☐ dexamethasone 1 mg/mL oral suspension

_____	_____	_____
PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

☐ Original Copy – Chart ☐ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1,13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12,13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5,6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9, Fig 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8,9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	8,9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8,9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8,9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11,12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10,11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	13

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Dexamethasone versus prednisone for children receiving asthma treatment in the pediatric inpatient population: protocol for a feasibility randomized controlled trial

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Dexamethasone versus prednisone for children receiving asthma treatment in the pediatric inpatient population: protocol for a feasibility randomized controlled trial

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Keywords: asthma, inpatient, prednisone, dexamethasone, feasibility, randomized controlled trial, pragmatic trial, compliance

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References: 18
Figure 1: Schematic of Study Design
Supplementary File 1: Physician Orders for Asthma in the ED order set
Supplementary File 2: Physician Orders for Asthma Respiratory Failure in the ED order set
Supplementary File 3: Emergency Department Nursing Medical Directive
Supplementary File 4: Study Order Sheet

ABSTRACT

Introduction

Asthma exacerbations are a leading cause of pediatric hospitalizations. Corticosteroids are key in the treatment of asthma exacerbations. Most current corticosteroids treatment regimens for children admitted with asthma exacerbation consist of a 5-day course of prednisone or prednisolone. However, these medications are associated with poor taste and significant vomiting, resulting in poor compliance with the treatment course. While some centers already use a short course of dexamethasone for treating children hospitalized with asthma, there is no evidence to support this practice in the inpatient population.

Methods and analysis

This single-site, pragmatic, feasibility randomized controlled trial, will determine the feasibility of a non-inferiority trial, comparing two treatment regimens for children admitted to the hospital and receiving asthma treatment. Children 18 months to 17 years presenting to a Canadian tertiary care centre will be randomized to receive either a short course of dexamethasone or a longer course of prednisone/prednisolone once admitted to the inpatient units. The primary clinical outcome for this feasibility study will be readmission to hospital, or repeat Emergency Department visits, or unplanned visits to primary health care providers for asthma symptoms within 4 weeks of hospital discharge. Feasibility outcomes will include recruitment and allocation success, compliance with study procedures, retention rate, and safety and tolerability of study medications. We plan on recruiting 51 children, and between-group comparisons of the clinical outcome will be conducted to gain insights on probable effect sizes

Ethics and Dissemination

Research Ethics Board approval has been obtained for this study. The results of this study will inform a multi-site trial comparing prednisone/prednisolone to dexamethasone in inpatient asthma treatment, which will have the potential to improve the delivery of asthma care, by improving compliance with a mainstay of treatment. Results will be disseminated through peer-reviewed publications, organizations and meetings.

Trial Registration:

Clinialtrials.gov: NCT03133897

Article Summary

Strengths and limitation of this study:

- This pragmatic feasibility trial paves the way for a large multi-site pragmatic trial which will compare a short course of dexamethasone to a longer course of prednisone / prednisolone in the treatment of patients admitted to the hospital with asthma symptoms.
- As patients are enrolled after the decision to admit to hospital has been made, there is no restriction on the type of corticosteroid prescribed by the Emergency Department physician on presentation, allowing for generalizability and applicability to most pediatric clinical settings.
- Participants and health care providers will not be blinded to the intervention; this will however allow for better generalizability and interpretation of results as palatability of

prescribed corticosteroids and length of treatment are known to affect compliance, which would both be lost with blinding.

List of Abbreviations

- CS: Corticosteroids
- CHEO: Children's Hospital of Eastern Ontario
- ED: Emergency Department
- IV: Intravenous
- POS: "Physician Orders for Asthma in the ED" and "Physician Orders for Asthma Respiratory Failure in the ED" order sets
- PI: Principal Investigator
- PRAM: Pediatric Respiratory Assessment Measure
- DSMB: Data Safety Monitoring Board
- REDCap: Research Electronic Data Capture
- AE: Adverse Events
- SAE: Serious Adverse Events

INTRODUCTION

Asthma is the most common chronic disease of childhood,[1] affecting approximately 15% of children and youth in Canada.[2] Asthma continues to be one of the leading cause of hospitalization in children.[3] In Ontario, the burden of illness related to asthma is enormous, accounting for one third of government health expenditures for the general population.[4]

A key element for treating children presenting with symptoms consistent with acute asthma exacerbations is the administration of systemic corticosteroids (CS). Systemic CS reduce the need for hospitalization and the risk of relapse after initial treatment, and may also facilitate an earlier discharge from the hospital.[5] Some centres already use a short course of dexamethasone for inpatient asthma management. However, while data is promising for outpatients, there is no evidence to support this practice in the inpatient population. Most current CS regimens for the treatment of children hospitalized with an asthma exacerbation consist of a 5-day course of prednisone or prednisolone.

There is evidence that 2 days of once daily dexamethasone is a least as effective as 5 days of prednisone for preventing relapse in outpatient pediatric asthma.[6] In addition, patients receiving dexamethasone are significantly less likely to experience vomiting in the ED and even after returning home.[6] Preliminary cost-estimates suggest that dexamethasone may save at least $3500 per 100 patients compared to traditional treatment with prednisone or prednisolone.[7]

Prednisone is only available in Canada as a tablet or compounded suspension, which limits use due to swallowing ability and accessibility. When compared to dexamethasone, prednisolone is associated with poor palatability and significant vomiting.[8] Both prednisone and prednisolone are associated with poor compliance. Prednisone and prednisolone are compounded with similar

recipes, and therefore have a similar taste. Compliance with 5 days of prednisone has been estimated in one study to be as low as 64% for pediatric asthma. [9] As determined by a systematic review conducted by the principal investigator (PI) of this current study (PROSPERO 2016:CRD42016041766), studies comparing dexamethasone to prednisone in hospitalized patients are lacking. Promisingly, a retrospective cohort study in pediatric inpatients hospitalized with asthma suggested that dexamethasone, when compared to prednisone/prednisolone, may result in a shorter length of hospital stay and reduced costs with no difference in number of transfers to intensive care or readmissions.[10]

Dexamethasone is a potent glucocorticoid with a long half-life, therefore concerns have been raised regarding its potential for adrenal suppression. However, a study of high-dose (~1.7 mg/kg) dexamethasone in acute asthma found no significant difference in adrenal function between single-dose dexamethasone and 5 days of oral prednisone at day 14.[11]

Given the importance of CS in the treatment of asthma, the significant decrease in relapse risk associated with their use, and the high prevalence of childhood asthma, there is a need to determine whether a better tolerated and more convenient CS can be used as first line therapy. Although outpatient data on this issue exists, extrapolating treatment regimens from the outpatient population may not be appropriate as hospitalized children represent a sicker group of patients than those discharged from the emergency department.
In order to determine whether dexamethasone is at least as effective as prednisone/prednisolone in the treatment of inpatient asthma, we propose a feasibility study, as a first step in the development of a future multi-site trial.
Specifically, we plan to determine the feasibility of a non-inferiority trial, comparing a short course of dexamethasone to the more traditional longer course of prednisone/prednisolone for children admitted to the hospital and receiving asthma treatment. We will determine the feasibility of:

1- Enrolling patients upon admission to hospital, after they receive their first dose(s) of CS in the ED
2- Asking patients and/or caregivers to complete a symptom diary weekly for 4 weeks
3- Reassessing patients 7 days after hospital admission day
4- Successfully completing phone follow up 4 weeks post-hospital discharge
5- Collecting health utilization data post-hospital discharge.

METHODS AND ANALYSIS

Trial design

This trial will be conducted at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario, Canada. Children with asthma, admitted from the emergency department (ED) to the clinical teaching units will be eligible for the study (see Figure 1 for schematic of study design). Trial recruitment commenced in February 2018. This protocol follows SPIRIT guidelines.

A pragmatic design[12] was chosen to strengthen the generalizability of our findings, as the effectiveness of the intervention is being tested across routine clinical practice. Blinding of the participants and members of the health care team will not be undertaken in this study. Since the

palatability of the CS is likely to affect compliance, making the taste of the CS similar to ensure blinding would decrease ability to detect a difference in compliance due to taste. Moreover, given the length of therapy for prednisone/prednisolone is longer than that of dexamethasone, introducing placebo doses to ensure similar length of treatment would also potentially impact compliance and undermine the ability to detect a difference between groups. Investigators, data analysts, and research assistant completing patient assessment at the follow-up visit will however be blinded to group assignment.

Eligibility Criteria

Inclusion Criteria

Participants must meet all of the inclusion criteria listed below to participate in the study:

- Children admitted during the study period who are receiving asthma treatment for acute respiratory exacerbation as determined by the admitting physician and/or his/her representative. Of note, given the pragmatic design of the study, and that clinicians cannot always establish a diagnosis of asthma with certainty when a child presents to the hospital, children receiving asthma treatment will be considered for this study.
- Children aged 18 months to 17 years of age
- Children who have received oral or intravenous (IV) CS in the ED prior to admission under the institution's "Physician Orders for Asthma in the ED" and "Physician Orders for Asthma Respiratory Failure in the ED" order sets (POS) or "Emergency Department Nursing Medical Directive" (see Supplementary Files 1, 2 and 3 respectively)
- Children who have received IV CS for a total duration ≤ 24 hours since first dose of steroid administration in ED
- Participants must be capable of giving informed consent or have an acceptable surrogate capable of giving consent on their behalf

Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation

- Children who received oral or IV CS in the ED prescribed in any other way than the institution's POS or Nursing Medical Directive as doses may not be standardized
- Children who have received more than one dose of oral CS prior to enrolment
- Children who received oral or IV CS in the previous 2 weeks
- Children with any of the following: unrepaired congenital heart disease, cardiac disorder, chronic lung diseases other than asthma, such as bronchopulmonary dysplasia or cystic fibrosis, neurological or neuromuscular disease, sickle cell disease
- Children presenting with stridor
- Children admitted to the Pediatric Intensive Care Unit
- Children whose caregivers do not understand English or French

Intervention

Study Medication Description – Dexamethasone

Children randomized to the dexamethasone group will receive the approximate pharmacologic equivalent of two doses (days) of dexamethasone 0.6 mg/kg/dose (maximum dose 16 mg per dose) as current evidence supports the use of this dose for the inpatient population.[10,13]

The standard dose of dexamethasone provided in the ED is 0.3 mg/kg, while the standard dose of prednisone/prednisolone is 2 mg/kg (maximum single dose 50 mg), which is approximately equivalent to 0.3 mg/kg of dexamethasone.[14] Once enrolled, children who received dexamethasone 0.3 mg/kg or prednisone 2 mg/kg in the ED will be administered a "top-up" dose of dexamethasone at 0.3 mg/kg (maximum dose 8 mg). They will then receive a dose of dexamethasone 0.6 mg/kg (maximum dose 16 mg) 24 +/- 6 hours after the initial CS dose received in the ED (see Supplementary File 4 for Study Order Sheet). The dexamethasone dose will be rounded to the nearest 0.25 mg upon initial prescribing. Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purposes of the pharmacist rounding to available dosage forms.
Children who have received IV methylprednisolone in the ED and who are randomized to the dexamethasone group will not receive a top-up dose upon study enrolment. They will receive one dose (day) of dexamethasone 0.6 mg/kg/dose (maximum dose 16 mg per dose) 24 hours after the initial dose of oral CS in the ED and at least 6 hours after the last dose of IV methylprednisolone (see Supplementary File 4 for Study Order Sheet).

Standard of Care Description- Prednisone / Prednisolone
Children randomized to the prednisone / prednisolone group will receive four doses (days) of prednisone / prednisolone 1 mg/kg/dose once daily (maximum single dose 50 mg) following the initial dose of CS received in the ED (see Supplementary File 4 for Study Order Sheet).The prednisone dose will be rounded to the nearest 0.5 mg upon initial prescribing. Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purposes of the pharmacist rounding to available dosage forms.

Children who have received IV methylprednisolone in the ED and are randomized to the prednisone / prednisolone group will receive four doses (days) of prednisone / prednisolone 1 mg/kg/dose daily (maximum dose 50 mg). Study medication will be given 24 hours after the initial dose of oral CS in the ED and at least 6 hours after the last dose of IV methylprednisolone (see Supplementary File 4 for Study Order Sheet).

Children in both groups will receive asthma standard of care as dictated by their treating health care team, in addition to the study drug.

Study outcomes
Primary clinical outcome for feasibility study
(1) Readmission to hospital for asthma symptoms, repeat ED visit within 4 weeks for asthma symptoms, or unplanned visits to primary health care providers for asthma symptoms.

Feasibility Outcomes
(1) Allocation success; proportion receiving assigned CS as per randomization group
(2) Recruitment success; number screened, number eligible, number enrolled
(3) Compliance with reporting symptoms in diary
(4) Retention rate: a) Proportion of patients coming back for follow-up visits; b) Proportion of

patients reached at 4-week follow-up
(5) Safety of each CS
(6) Tolerability of each CS

Clinical outcomes for multicenter study:
The primary outcome for the multicenter study will be finalized following the feasibility study. As such, clinically relevant outcomes that will be measured in this feasibility study include:
(1) Readmission to hospital for asthma symptoms 4 weeks of ED presentation determined using parent report, and CHEO chart review
(2) Repeat ED visits for asthma symptoms within 4 weeks of ED presentation determined using parent report, and CHEO chart review
(3) Unplanned visits to physicians / nurse practitioners for asthma symptoms measured by parent report, and CHEO chart review
(4) Pediatric Respiratory Assessment Measure (PRAM) as measured on day 7 by a research nurse or study team physician. The PRAM score is a validated and reliable tool used to determine asthma severity in children.[15] Using PRAM score, rather than symptom recurrence, is more precise as a measure of symptom severity and has been used in a recent outpatient pediatric asthma RCT comparing dexamethasone and prednisolone.[16]
Health utilization data (readmissions, ED visits, unplanned visits to family physicians) will be determined through phone recall and health records.
(5) Number of children completing assigned CS treatment
(6) Asthma symptom frequency as measured by diary
(7) Length of hospital stay in hours
(8) Vomiting associated with CS administration as determined by parental interview and medical record review

Enrollment and Screening
A research assistant will review the list of admissions for the previous 12 hours, on a twice daily basis, from Monday to Friday. The research assistant will then ask a member of the patient's health care team (bedside nurse, charge nurse, resident, staff physician) to ask the family members for permission to approach the family about the study. The research assistant will then complete a screening log and maintain a phone follow-up ledger for consented patients. If the patient is eligible and the family gives their informed consent, and the child their assent if appropriate, they will be allocated to one of the study groups. Once written, informed consent has been obtained, the research assistant will communicate with the health care team to ensure the patient continues on the CS he/she has been randomized to, for the appropriate number of doses as determined by CS group assignment. A record will be kept of all screened patients, patient eligibility, allocation, and follow up to allow reporting according to CONSORT guidelines.[17]

Randomization and baseline visit (hospitalization)
After enrollment, the patients will be randomly allocated to one of the two treatment groups (day 0). The randomization schedule will have been previously generated using a computer. Randomization will be blocked with randomly chosen block lengths of 4 or 6. Treatment assignments will be written on a piece of paper and concealed in sequentially numbered opaque envelopes kept in a secure locked location in the study research office. The PI and analyst will

be blinded to the treatment intervention, but the research assistant in charge of screening and randomizing patients, as well as the patient's treating team (physicians and nurses) will not because of the pragmatic nature of the trial. Demographic data will be collected at baseline.

Follow up visit

Patients will be reassessed 7 days after admission day to hospital, +/- 3 days to allow for flexibility with patient's schedule, weekends, holidays and unexpected events. Patients will receive a physical examination by a study physician, and an assessment of asthma symptom severity through the PRAM score[15]. At that visit, we will collect compliance data with both courses of treatment, and remind participants to begin charting asthma symptoms in their symptom diary. PRAM scores at the follow up visit will be collected on the case report form. Data on Adverse Events (AE) and Serious Adverse Events (SAE) will also be collected at that visit. Patients unable to come back for the day 7 visit will receive a phone call from a study physician to ensure the family has no concerns, and compliance data with course of treatment will be collected via phone. If the participant consents, a partial PRAM assessment will be done via video conference call by the study physician.

Phone follow up

Phone follow up will be performed at 4 weeks post-hospital discharge, +/- 7 days to allow for flexibility with patient's schedule, weekends, holidays and unexpected events. Data on return visits to health care providers, ED visits and hospital readmissions will be collected by phone 4 weeks post-hospital discharge, as well as data on AE and SAE. We will also collect compliance data with both courses of treatment if the information could not be obtained earlier.
Data on patients' experience with prescribed CS will also be collected at the follow up phone call via semi-structured phone interviews.

Chart review

At the end of each subject's participation period, the research assistant will review the medical chart and extract information on treatment course in the Emergency Department and on the inpatient ward, including date, time, and dosage of CS and antibiotics administered. Data on length of stay will also be obtained. Charts will also be reviewed for subsequent visits to the ED, and for admissions for asthma symptoms in the 4 weeks following hospital discharge.

Expected duration of participant participation

Study subjects are expected to participate in the study from enrollment until 4 weeks after hospital discharge (see Figure 1)
Parents and/or caregivers in both study groups will be asked to electronically complete a standardized validated symptom diary weekly, starting 7 days post discharge until 4 weeks post discharge (The Asthma Quiz for Kidz). Patients who prefer a paper copy of the questionnaire will be provided with 4 questionnaires prior to hospital discharge, as well as preaddressed stamped envelopes to facilitate mailing back of the questionnaire. The Asthma Quiz for Kidz is a short 6-item questionnaire validated for in French and English for children aged 1 to 17 years.

Formulation, Packaging and Labelling

Dexamethasone

Patients will receive dexamethasone orally as tablet(s) or compounded suspension based on patient or health care provider preference. The dexamethasone suspension will be compounded at the CHEO research pharmacy using a combination of dexamethasone sodium phosphate USP injection 10mg/mL ([PR]Dexamethasone Omega Unidose; see product monograph) manufactured by Omega Laboratories Ltd. and Ora-Blend®, a flavored oral suspending vehicle manufactured by Galenova Inc. The compound is created by combining 10mL of the dexamethasone 10mg/mL sodium phosphate USP and 90mL of Ora-Blend®. The final oral suspension has a concentration of 1mg/mL of dexamethasone and a pinkish hue with a milky consistency. The appropriate dose for the participant will be drawn up into an oral syringe, which will be labeled for investigational use.

Prednisone / Prednisolone

Patients will receive prednisone/prednisolone orally as tablet(s) or compounded suspension (prednisone) or as a commercially available liquid (prednisolone). The prednisone suspension will be compounded at the CHEO research pharmacy using a combination of APO-prednisone 50 mg tablets ([PR]APO-PREDNISONE 50 mg tablet; see product monograph) and Syrup, NF (Simple) a sweetened vehicle manufactured by Medisca at a ratio of one 50 mg tablet for every 10 mL of Syrup, NF (Simple). The final oral liquid has a concentration of 5 mg/mL with a yellow to white hue and clear to milky consistency. The appropriate dose for the participant will be drawn up into an oral syringe, which will be labeled for investigational use.

Sample Size Determination

We sought a sample size that would allow us to estimate our feasibility outcomes with reasonable precision. As such, we have set out to achieve a 15% margin of error (i.e. half-width of 95% confidence interval=0.15) for any proportions to be estimated (e.g. allocation success, retention success). At a hypothesized proportion of 50%, we determined that 43 patients will be needed to achieve this level of precision. This provides a most conservative estimate since any proportions other than 50% will require fewer patients. Factoring in an additional 15% of patients as allowance for attrition or incomplete data we will set a recruitment target of n=51 in total. With approximately 18 asthma admissions per month, assuming 70% are eligible and 50% of eligible patients consent, we expect to meet this sample size requirement in 9 months.

Quantitative Data Analysis

For all relevant feasibility outcomes, binary proportions (e.g. % success) and the associated 95% confidence interval will be estimated using the Wilson method. To help inform the design of main trial (i.e. expected effect sizes), we will apply intention-to-treat principles and estimate the treatment effect (and 95% CI) by comparing outcomes (proposed for the main trial) between intervention groups using statistical techniques appropriate to the type and distribution of the various outcomes (e.g. continuous, binary, count data).

Qualitative Data Analysis

Semi-structured interviews at week 4 will be audio taped and transcribed verbatim. Analyses will be conducted using Nvivo 9 software. Inductive analysis will be used to identify categories, patterns and themes.[18]

Role of the Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be set up for this study. An initial meeting will occur prior to enrolling the first patient to determine the terms of reference, review Health Canada-mandated SAE reporting and safety outcomes. Given that this trial is a feasibility trial as opposed to an efficacy trial, no interim analysis for efficacy will be performed. The DSMB will meet every 4 months after the initial meeting, until study completion. Study results will be analyzed after all participants have completed the study.

SAFETY AND ADVERSE EVENTS

Patient safety will be ensured by using standard pediatric dosing[10,13], by adhering to the inclusion and exclusion criteria, and by following the current standard of care for mitigation of treatment side effects. Patients whose PRAM scores are greater than 1 on follow up visits will be treated appropriately. A follow-up with a study physician will be booked if necessary. The patient's family physician will also be contacted to ensure appropriate follow up. The patient's family will be instructed to come to the ED immediately in the case of symptom worsening, and to page the study physician who assessed the patient. Patients whose PRAM scores are greater than 3 on follow up visits will be immediately sent to the CHEO ED.
Patients unable to come back for the day 7 visit will receive a phone call from a member of the study team to ensure the family has no concerns. If health concerns are identified, patients will be asked to come to CHEO to be assessed by a member of the study team. If the family refuses, patients will be encouraged to visit the closest ED or to visit their family physician. A member of the investigative team will also call the family physician's office to ensure the patient is seen promptly.

MONITORING

The investigator will ensure the trial is adequately monitored in accordance to the protocol and applicable regulatory requirements. An internal monitoring visit will be completed by the CHEO Research Institute Quality Assurance (QA) team after the first participant is enrolled and further monitoring by the Quality Assurance team can be requested by the investigator, if required. Peer review, on-site monitoring visits will be completed by an investigator-appointed monitor who is familiar with the study medication and protocol. The monitor will ensure that the trial is conducted and documented according to Good Clinical Practices. As a Health Canada regulated trial, this study may be inspected at any time by Health Canada.

DATA HANDLING AND RECORD KEEPING

Data Management Responsibilities

Information will be collected for each participant by a member of the research study team at each point of study data collection. Participants will be assigned a randomization code at baseline and their records will be identified using this code so that all study subjects are non-identifiable by their study documents.

The PI and research assistant will be responsible for the overall supervision of the study. The research assistant will be responsible for recruiting patients, communicating with the nursing staff to ensure patients receive the right CS after the initial dose received in the ED, supervising the chart review and conducting the phone follow ups. Study team physicians will be responsible for patient reassessment 7 days after initial presentation.

Subject data will be recorded on source documents and transferred to REDCap (Research Electronic Data Capture). REDCap is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) 128 bit encryption between the data entry client and the server (https); 3) audit trails for tracking data manipulation and export procedures; 4) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 5) procedures for importing data from external sources; and 6) advanced features, such as branching logic and calculated fields.
REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at CHEO. The application and data are housed on servers provided by CHEO. These servers are located within CHEO's secure data centre. The data centre is physically secured through limited badge access and security cameras. Local support for REDCap is provided by CHEO's Clinical Research Unit.

Confidentiality
All participant related information including Case Report Forms, laboratory specimens, reports etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have access to the records. Participants will be identified only by means of a coded number specific to each participant. All computerized databases will identify participants by numeric codes only and will be password protected or encrypted.

Upon request, participant records will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of a participating pharmaceutical sponsor and applicable regulatory agencies such as Health Canada or The Food and Drug Agency.

Record Retention
All research records will be retained for 25 years after closure as required by Health Canada. All study documentation will be kept in a secure location at the study site.

Data Safety Monitoring Board (DSMB)
This study will be monitored by an independent DSMB, consisting of an independent physician, and two other members not involved in this study. The DSMB will be immediately informed of any serious SAE which may potentially be study drug related. Other SAEs will be reviewed during regular DSMB meetings. Interim reports, prepared by the data management team for the study, for review by the DSMB will include data on recruitment, compliance, adverse effects, baseline comparability and treatment comparisons. An agreed upon blinded review package which contains the appropriate data summary by treatment will be provided by the study statistician for the purposes of these reviews. The review package could then be unblinded at the request of the DMSB.

Patient and public involvement

Patients and the public were not directly involved in the design of the study. The intervention was chosen on the basis of studies reporting poor compliance with current CS used in the treatment of inpatient asthma [9] due to poor palatability of the drug and associated vomiting.[8] Study results will be disseminated through patients and study participants through our institution's social media platform.

Ethical Considerations

This study will be conducted in full conformance with the principles of the 'Declaration of Helsinki', GCP and within the laws and regulations of Canada (Health Canada, Food and Drug Act, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects).

Protocol and amendments will be submitted to the CHEO REB for formal approval to conduct the study. The decision of the REB concerning the conduct of the study will be made in writing to the investigator.

All participants for this study will be provided a consent form and assent form if applicable, describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. These consent and assent forms were submitted with the protocol for review and approval by the REB. The formal consent of a participant, using the REB-approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form must be signed by the participant or legally acceptable surrogate and the investigator-designated research professional obtaining the consent. Patients will be free to withdraw from study participation at any point in time and will receive the same standard of medical care given to all patients admitted with asthma to the pediatric ward at CHEO. The data collected during this trial will be held confidential.

All study investigators will have access to the final trial dataset. The International Committee of Medical Journal Editors authorship eligibility guidelines will be used for publication. We plan on disseminating our study results through peer reviewed publications, professional organizations and conferences.

Author Contributions

Catherine Pound conceived and designed the study and drafted the first version of the manuscript, and approved the final version of the manuscript.
Jaime McDonald participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Ken Tang participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Gillian Seidman participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Radha Jetty participated in the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.
Sarah Zaidi participated in revising the study protocol, read and reviewed the manuscript and approved the final version of the manuscript.
Amy Plint participated in and supervised the design of the study, read and reviewed the manuscript and approved the final version of the manuscript.

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The authors wish to thank Ms Sheila Ledoux and Ms Sabrina Hamer for their help with quality assurance and help with protocol submission to Health Canada.

Competing Interests:
None of the authors have any competing interests to disclose

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Data sharing
Data collection forms can be requested through the corresponding author.

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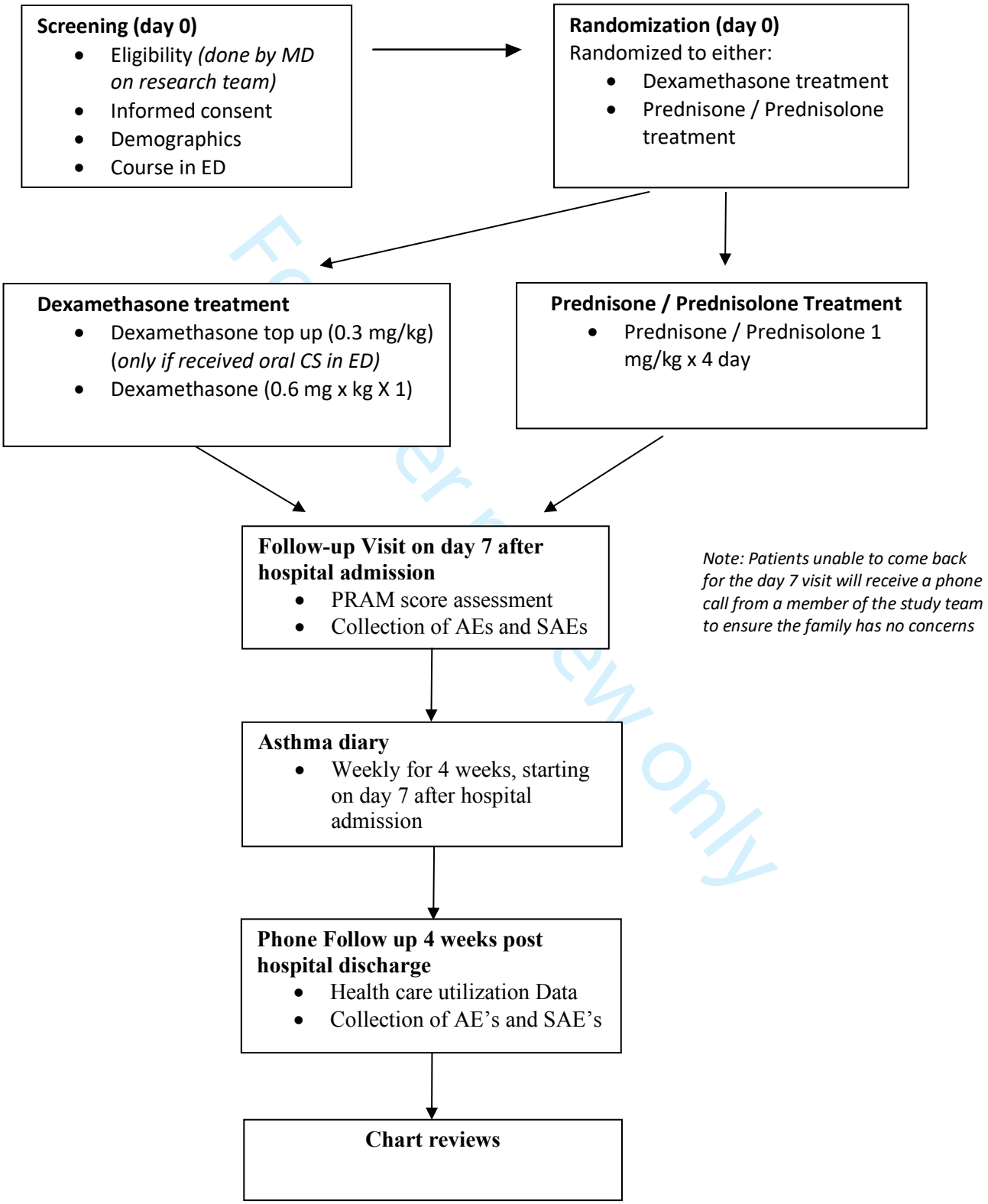
Figure 1
Schematic of Study Design



Physician Orders for Asthma in the ED [250]

For severe respiratory distress/signs of respiratory failure OR Failure to improve after 1 hour of treatment select Order Set # 251 Asthma - Severe Respiratory Distress/Failure to Improve after initial treatment.

General

CHEO NURSING INTERVENTION PRE SEND PATIENT WITH MED

☑ Send Patient home with Medications	Until discontinued, Starting today Unused portion of the Salbutamol MDI may be dispensed to the patient upon discharge

CHEO NURSING ASSESSMENT PRE ASTHMA PATHWAY

☐ Pathway Initiation	Until discontinued, Starting today Pathway: Asthma

Respiratory

CHEO RESPIRATORY INTERVENTIONS PRE O2 92% NO COMMENTS

☐ Oxygen Therapy	Until discontinued, Starting today SpO2 Target (equal to or greater than): 92%

Medications

For PRAM (Pediatric Respiratory Assessment Measure) Score of 1 - 3 (mild)

☐ Salbutamol MDI — **"And" Linked Panel**

☐ salbutamol 100 mcg/puff MDI PRN DOSE	Inhalation, Every 30 minutes PRN, Starting H+3 Hours PRN FREQUENCY. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

For PRAM Score of 4-7 (moderate)

☐ Salbutamol MDI 100 mcg/puff

☐ salbutamol 100 mcg/puff MDI - Select ONLY if not already ordered as per medical directive	Inhalation, Every 20 minutes, For 3 Doses (If not already given as per medical directive) Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.
☐ salbutamol 100 mcg/puff MDI PRN DOSE	Inhalation, Every 30 minutes PRN Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.

For PRAM score of 8-12 (severe)

☐ Salbutamol/Ipratroprium Nebules - Select ONLY if not already ordered under medical directive

Select ONLY if not already ordered under medical directive.

☐ salbutamol inhalation solution	Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ ipratropium 250 mcg/2 mL inhalation solution	250 mcg, Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.

☐ Salbutamol Nebules/MDI **"Or" Linked Panel**

After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI

☐ salbutamol inhalation solution	Nebulization, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ salbutamol 100 mcg/puff MDI	Inhalation, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.

Physician Orders for Asthma Respiratory Failure in the ED [251]

For severe respiratory distress/signs of respiratory failure OR failure to improve after 1 hour of treatment from Order Set 250 - Asthma

General

CHEO NURSING ASSESSMENT PRE ASTHMA PATHWAY

☐ Pathway Initiation	Until discontinued, Starting today Pathway: Asthma

CHEO VITAL SIGNS PRE ASTHMA ED

☑ Blood pressure	Every 5 min During magnesium infusion
☑ Cardio Respiratory Monitor with Oxygen Saturation	Continuous

Respiratory

CHEO RESPIRATORY INTERVENTIONS PRE O2 95% NO COMMENTS

☑ Oxygen Therapy	Until discontinued, Starting today SpO2 Target (equal to or greater than): > 95%

Labs

CHEO BLOOD PRE ED ASTHMA

☑ CBC and Differential	Once
☑ Electrolytes (Whole Blood)	Once
☑ Blood Gas Capillary	Once

IV fluids

IV FLUIDS

☐ 0.9% NaCl bolus	Intravenous, Once, For 1 Doses
☐ D5-0.9% NaCl IV solution	Intravenous, Continuous

Medications

For PRAM score of 8-12 (severe)

☐ Salbutamol/Ipratroprium Nebules - Select ONLY if not already ordered under medical directive

Select ONLY if not already ordered under medical directive.

☐ salbutamol inhalation solution	Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ ipratropium 250 mcg/2 mL inhalation solution	250 mcg, Nebulization, Every 20 minutes, Starting today, For 3 Doses If not already given as per medical directive.

☐ Oral steroid - Select ONLY if not already ordered under medical directive. (Single Response)

Select ONLY if not already ordered under medical directive.

○ dexamethasone phosphate 1 mg/mL suspension (CHEO) - FIRST choice	0.3 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 0.3mg/kg/dose, MAX 10 mg.
○ predniSONE tablet - FIRST choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ prednisoLONE 1 mg/mL solution - SECOND choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
○ predniSONE 5 mg/mL suspension (CHEO) - LAST Choice	2 mg/kg/dose, Oral, Once, For 1 Doses If oral steroid not already given as per medical directive. Usual dose: 2 mg/kg/dose. MAX 50 mg.
☐ Salbutamol Nebules/MDI	**"Or" Linked Panel**
After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI	
☐ salbutamol inhalation solution	Nebulization, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: 3 to 6 kg: 0.625 mg = 1/2 of a 1.25 mg nebule (administer with 2 mL 0.9 % NaCl), 6 - 12 kg: 1.25 mg 12 - 20 kg: 2.5 mg Greater than 20 kg: 5 mg
☐ salbutamol 100 mcg/puff MDI	Inhalation, Every 30 minutes PRN After initial 3 salbutamol nebulizations, if clinically improving change to salbutamol MDI. Usual dose: Less than 6 kg: 200 mcg 6 - 16 kg: 400 mcg 16 - 24 kg: 600 mcg 24 - 34 kg: 800 mcg Greater than 34 kg: 1000 mcg Give via spacer device.
Other Medications	
☐ methylPREDNISolone (PF) 62.5 mg/mL injection	1 mg/kg/dose, Intravenous, Once, For 1 Doses Usual dose 1 - 2 mg/kg/dose, MAX 125 mg. If prednisoLONE or prednisONE already given as per medical directive, limit methylPRENISolone dose to 1 mg/kg/dose, MAX 125 mg.
☐ magnesium sulfate in 0.9% NaCl 40 mg/mL injection	50 mg/kg/dose, Intravenous, Once, For 1 Doses Usual dose: 50 mg/kg/dose, MAX 2000 mg. Give IV over 20 - 30 minutes.

CHILDREN'S HOSPITAL OF EASTERN ONTARIO

1. **Name of the Medical Directive:** Initial oral steroid for known asthmatic patients with moderate to severe respiratory distress in the Emergency Department

Approval Status (Dates)

Version/Revision	MDC Submission	MDC Approval
Version 1	Nov 30, 2009	Dec 11, 2009
Version 2	Aug 1, 2010	Aug 10, 2010
Version 2.1	Nov 9, 2012	
Version 3	July 14, 2014	October 22, 2014
Version 4	November 2017	

Effective Date: December 11, 2017 **Directive Number: 2022**
Renewal Frequency: ☐ 3 years ☑ Other (may not exceed 3 years):
Expiry Date: March 31, 2018

2. **Contact Information**
Area of Practice: Emergency Department
Medical Director: Medical Director, Emergency Department **Extension:** 2899
Developed By: Dr. Roger Zemek **Extension:** 2318

3. **Purpose Statement**
This medical directive allows nurses (RN) or respiratory therapists (RRT) to initiate and administer an oral steroid dose to Emergency Department (ED) patients with a history of asthma presenting with moderate to severe asthma exacerbations. Oral corticosteroids are the gold standard treatment in children and adults presenting with moderate to severe asthma to the emergency department, reducing by 25% the risk of hospital admission when administered within an hour of triage. This will allow the initiation of therapy for patients with moderate to severe asthma exacerbations prior to assessment by the physician. Choice of medication will be determined by whether the patient can swallow tablets (prednisone) or needs a liquid suspension (dexamethasone, prednisolone, prednisone – determined by medication availability). Dosage of medication will be dictated by the patient's weight. Patient eligibility will be determined by the patient's Pediatric Respiratory Assessment Measure (PRAM) score upon arrival to the ED.

4. **Personnel Authorized to Implement the Medical Directive**
- All staff, following appropriate orientation, must demonstrate the knowledge, skill and judgement required to apply the medical directive
  - RN hired in the ED
  - RN on the Float Team who have received training/orientation and are working in the ED
  - RRT working in the ED

5. **Patient Population and Indications**
- Alert and oriented
- Aged 1 to 17 years
- History of asthma with the use of bronchodilator(s) for prior exacerbations
- Triage PRAM (Pediatric Respiratory Assessment Measure) score of 4 to 11.

6. **Contraindications**
- PRAM score < 4
- CTAS (Canadian Triage and Acuity Score) 1 or PRAM = 12
- Any use of oral corticosteroid in the past 14 days – **DISCUSS WITH MD FIRST**
- Three prior courses of oral steroids in the past year – **DISCUSS WITH MD FIRST**
- Hypersensitivity to prednisone, prednisolone, dexamethasone or oral corticosteroids
- Patients meeting any exclusion criteria from the asthma critical pathway
- Patients with respiratory condition such as bronchopulmonary dysplasia and cystic fibrosis
- Patients with cardiac, metabolic, immunological disease, or history of adrenal suppression
- Patients with co-existing acute illness such as pneumonia, pertussis, or croup
- Exposure to varicella in the previous 3 weeks in a susceptible child.

7. Description of the Procedure

a) Identify ED patients with breathing difficulty and a history of asthma, as per the Asthma critical pathway inclusion/exclusion criteria

b) Complete a respiratory assessment using PRAM (see below) and baseline vital signs, and document within the appropriate sections of the patients health record.

c) Weigh the patient and document

d) Determine the appropriate CTAS and treatment regimen based on the patient's PRAM

- ❑ PRAM score 1 – 3: patient will be managed per the initial bronchodilator medical directive only
- ❑ PRAM score 4 – 11: patient will be managed per the initial bronchodilator medical directive and receive one dose of oral steroid, as per the dosing in the table below. This will be given as prednisone tablets, dexamethasone elixir, elixir, prednisolone suspension, or prednisone suspension (depending on drug availability) immediately following the first bronchodilator treatment and before the second dose of the initial three back to back bronchodilator treatments. (Specifically, the patient will receive the 1st inhaled treatment, then oral psteroid, then the 2nd inhaled treatment, and then their 3rd inhaled treatment).
- ❑ PRAM score 12: notify physician immediately for consideration of IV corticosteroid

e) **Any questions regarding the appropriateness or dosage of prednisone/prednisolone/ dexamethasone should be discussed with the physician prior to administration.**

f) **When an RN and RRT are working together to provide care for the patient, they must verbally communicate the assessment, plan and medications administered with each other, in addition to documenting within the electronic medication administration record (eMAR).**

g) **If at any time the patient no longer responds appropriately to treatment or deteriorates, immediately notify the physician.**

PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM)

	0	1	2	3
Suprasternal Indrawing	absent		present	
Scalene retractions	absent		present	
Wheezing	absent	expiratory	inspiratory and expiratory	Audible without stethoscope/ absent with no air entry
Air entry	normal	decreased at bases	widespread decrease	absent/ minimal
Oxygen saturation	≥ 95%	92%-94%	< 92%	

Severity Classification	PRAM Clinical Score
Mild	1 – 3
Moderate	4 – 7
Severe	8 – 12
Impending Respiratory Failure	12 plus following lethargy, cyanosis, decreasing respiratory effort, and/or rising $pC0_2$

MEDICATION DOSAGES

Prednisone Oral 5 or 50mg Tablets
2 mg / kg to a maximum of 50 mg (round up to the nearest 5 mg)
Dexamethasone Oral Elixir (1st choice if available) (1 mg / 1 ml)
0.3 mg / kg to a maximum of 10 mg (round up to the nearest 1 mg)
Prednisolone Oral Suspension (2nd choice if available) (1 mg / 1 ml)
2 mg / kg to a maximum of 50 mg (round up to the nearest 1 mg)

Prednisone Oral Suspension (last choice) (5 mg / 1 ml)
2 mg / kg to a maximum of 50 mg (round up to the nearest 1 mg)

8. Consent and Documentation

- Verbal consent will be obtained from the patient/parent prior to administration of the medication. Any refusal of treatment will be documented. Documentation of the medication, indicating "as per medical directive #2022", will be made in the patient's health record, as appropriate

9. Quality Management Process

- All RNs and RRTs will be educated about the purpose, indications and contraindications, and possible complications for administration of oral prednisone/prednisolone/dexamethasone by the clinical educator or delegate.
- All safety reports related to the administration of oral prednisone/prednisolone under this medical directive will be reviewed by the clinical manager, director and medical director. A copy will be forwarded to the Chair of the Medical Directives Committee.
- Prior to renewal of this medical directive, audits will be conducted to verify that the medical directive is being used appropriately.

10. References and Resources

- CHEO:
  - Medical Directives Policy
  - Medical Directive # 2017 – Initial bronchodilator therapy for known asthmatic patients in the Emergency Department
- College of Nurses of Ontario (CNO):
  - Practice Guidelines:
    - Authorizing Mechanisms (rev. November 2013)
    - Consent (rev. June 2009)
    - Directives (rev. November 2011)
  - Practice Standards:
    - Decisions About Procedures and Authority, Revised 2013
    - Documentation, Revised 2008 (rev. June 2009)
    - Medication, Revised 2014
    - Professional Standards, Revised 2002 (rev. June 2009)
  - The Regulated Health Professions Act (RHPA): Scope of Practice, Controlled Acts Model (2011)
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Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'Est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol: June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to predniSONE/prednisoLONE:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

_____ **predniSONE** or **prednisoLONE** _____ mg (1 mg/kg/dose; MAX 50 mg**; Dose to be rounded to the nearest 0.5 mg upon initial prescribing**) PO daily x 4 days starting 24 hours after first dose in Emergency Department (ED), and at least 6 hours after dose of IV steroids in ED.

For Pharmacy Use Only – Dispense:

- □ predniSONE 1 mg tablet
- □ predniSONE 5 mg tablet
- □ prednisone 50 mg tablet
- □ predniSONE 5 mg/mL oral suspension
- □ prednisoLONE 1 mg/mL oral solution

PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

□ Original Copy – Chart □ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to dexamethasone:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

TOP UP DOSE ***(for patients receiving prednisone/prednisolone OR dexamethasone in ED to a target of 0.6 mg/kg TOTAL dexamethasone or equivalent)***

NOTE: Please verify steroid and mg/kg dose in EPIC before ordering. If patient received dexamethasone 0.6 mg/kg/dose (OR more than 16 mg) in ED or IV steroids, **DO NOT GIVE TOP UP DOSE**. Standard doses according to the ED Medical Directive are 0.3 mg/kg/dose of dexamethasone (MAX 10 mg) and 2 mg/kg/prednisone/prednisolone (MAX 50 mg).

IF RECEIVED DEXAMETHASONE IN ED:

Dose: _____ mg ÷ _____ kg (pt weight) = _____ (A) mg/kg/dose

□ Top-up dose **NOT REQUIRED** (received 0.6 mg/kg/dose OR greater or equal to 16 mg in ED)

□ Top-up dose **REQUIRED** (_____ mg (0.6 mg/kg/dose) - _____ (A) mg/kg/dose = _____ (B) mg/kg/dose)

_____ **Dexamethasone** ____ mg (_____ (B) mg/kg/dose; MAX 16 mg/dose **INCLUDING** dose received in ED; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 STAT upon randomization

THEN

_____ **Dexamethasone** ____ mg (0.6 mg/kg/dose; MAX 16 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 dose 24 hours after first dose of **steroid** in ED

For Pharmacy Use Only – Dispense:

□ dexamethasone 0.5 mg tablet

□ dexamethasone 4 mg tablet

□ dexamethasone 1 mg/mL oral suspension

_____	_____	_____
PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

□ Original Copy – Chart □ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Children's Hospital of Eastern Ontario
Centre hospitalier pour enfants de l'est de l'Ontario

PHYSICIAN ORDERS
FOR
Study Protocol:
dexamethasone versus predniSONE for asthma treatment in the pediatric inpatient population; a feasibility study.

Protocol June 2018
CHEOREB#17/08E

Patient Identification

Study ID #: PredDex-_____

Allergies: _____ Weight: _____ kg

First dose of systemic corticosteroid in ED received at (date and time): ___/____/_____ ___:____

_____ ***Randomized to dexamethasone:***

*Deviations of up to 10% of the recommended mg dose per kilogram will be permitted for the purpose of the pharmacist rounding to available dosage forms

_____ Discontinue oral steroid treatment for asthma ordered upon admission (to avoid duplication of therapy)

TOP UP DOSE ***(for patients receiving prednisone/prednisolone OR dexamethasone in ED to a target of 0.6 mg/kg TOTAL dexamethasone or equivalent)***

Patient who received IV steroids in ED do not qualify for top up dose.

NOTE: Please verify steroid and mg/kg dose in EPIC before ordering. Standard doses according to the ED Medical Directive are 0.3 mg/kg/dose of dexamethasone (MAX 10 mg) and 2 mg/kg/prednisone/prednisolone (MAX 50 mg).

IF RECEIVED PREDNISONE/PREDNISOLONE IN ED:

_____ **Dexamethasone** ____ mg (0.3 mg/kg/dose; MAX 8 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 STAT upon randomization

THEN

_____ **Dexamethasone** ____ mg (0.6 mg/kg/dose; MAX 16 mg; **Dose to be rounded to the nearest 0.25 mg upon initial prescribing**) PO x 1 dose 24 hours after first dose of **steroid** in ED

For Pharmacy Use Only – Dispense:

- ☐ dexamethasone 0.5 mg tablet
- ☐ dexamethasone 4 mg tablet
- ☐ dexamethasone 1 mg/mL oral suspension

_____	_____	_____
PHYSICIAN SIGNATURE	PRINT NAME OF PHYSICIAN	DATE & TIME

☐ Original Copy – Chart ☐ Copy to Pharmacy Date: July 2018 Created by: DG/RV

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1,13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12,13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5,6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	11
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8,9, Fig 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8,9
Allocation concealment	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed	8,9

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8,9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8,13
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8,9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11,12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10,11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset,	13

		and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	8
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A