

**Protocol Title:** Oral Dexamethasone for the Treatment of Acute Migraine Recurrence in Pediatric Patients Presenting to the Emergency Department with Migraine: A Pilot Randomized Controlled Trial

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# **1. General Information**

## **1.1. Name and Address of the Sponsor**

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## **1.2. Name and Address of the Person Authorized to Sign the Protocol and Amendments**

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## **1.4. Name and Title of Investigators Responsible for the Trial and The Address and Telephone Numbers for the Trial Site**

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**1.5. Name and Address of the Qualified Physician who is Responsible for Trial-Related Medical Decisions**

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**1.6. Name and Address of the Clinical Laboratory and Research Pharmacy Involved in the Trial**

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## **Investigator Agreement**

By signing below, I confirm that I have read this protocol and agree to conduct this study in accordance with the procedures described in this protocol, with Good Clinical Practice and

Health Canada Food & Drug Act, Part C, Division 5 of the Regulations: Drugs Trials Involving Human participants

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

**Signature of Principal Investigator** \_\_\_\_\_

**Date** \_\_\_\_\_

**Site Address**

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## **2. Abbreviations**

AE – Adverse event

CHEO – Children’s Hospital of Eastern Ontario

CRF – Case report form

ED – Emergency Department

ICH – International Conference on Harmonization

MICYRN – Maternal, Infant, Child and Youth Research Network

REB – Research Ethics Board

REDCap – Research Electronic Data Capture

SOP – Standard Operating Procedures

SUPPORT – Students Undertaking a Pediatric Program of Research Training

### 3. Study Summary

<b>Title</b>	Oral Dexamethasone for the Treatment of Acute Migraine Recurrence in Pediatric Patients Presenting to the Emergency Department with Migraine: A Pilot Randomized Controlled Trial
<b>Short Title</b>	A Pilot Trial on the Use of Oral Dexamethasone for Preventing Pediatric Migraine Recurrence
<b>Protocol Number</b>	N/A
<b>Phase</b>	Phase 3
<b>Methodology</b>	Randomized, double-blind, 2-arm parallel group trial
<b>Study Duration</b>	6 months
<b>Study Center(s)</b>	Single center: Children's Hospital of Eastern Ontario
<b>Objectives</b>	To determine the feasibility of carrying out a multicenter randomized controlled trial to assess the efficacy of oral dexamethasone for preventing migraine recurrence in the pediatric ED through the implementation of a pilot randomized trial. The primary scientific objective will be to determine if oral dexamethasone is superior to placebo in preventing migraine recurrence within 48 hours of ED discharge amongst pediatric patients presenting to the ED with migraine.
<b>Number of Participants</b>	20
<b>Diagnosis and Main Inclusion Criteria</b>	Children and adolescents aged 8-18 years with migraine according to modified International Classification of Headache Disorders 3 <sup>rd</sup> edition (beta version) criteria
<b>Study Product, Dose, Route, Regimen</b>	Dexamethasone 0.6mg/kg PO as a one time dose given in the emergency department (maximum of 15mg)
<b>Duration of administration</b>	Single dose in the emergency department
<b>Reference therapy</b>	Placebo



<b>Statistical Methodology</b>	The primary outcome pertains to comparing the proportion of patients in each group with headache recurrence. A Fisher's exact test will be used to compare the two groups on the primary outcome and on the secondary outcomes that involve proportions. Adverse events will be presented descriptively in tabular form, with the frequency and percentage of each adverse event listed by the corresponding group.
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## 4. Background Information and Clinical Data

Headache is very common in the pediatric population, with an estimated worldwide prevalence of 58.4% amongst children and adolescents(1). Given its prevalence, it is not surprising that it accounts for a significant proportion of pediatric emergency department (ED) visits: anywhere from 0.8-1.3% of all pediatric ED visits are due to headache(2-5). Although the majority of pediatric ED visits for headache are due to secondary causes, migraine accounts for between 5.4% and 28.7% of these visits(2-6).

Relapse of migraine shortly after the initial ED visit appears to be a very common phenomenon. Studies report that anywhere from 26% to 68% of pediatric migraine patients have relapse of their migraine within one week of ED discharge, even when the pain was initially successfully treated in the ED(7-9). A recent study of 32,124 pediatric patients presenting to the ED with migraine found that 5.5% of these patients had a return visit to the ED within 3 days(10). Although the proportion of patients with return visits is relatively small, when considered in the context of the volume of pediatric ED visits for migraine, it represents a significant burden to the health care system. In addition, migraine relapse is recognized as being a very important outcome to consider in the design of acute migraine therapy trials. The International Headache Society guidelines for controlled trials of drugs in migraine list incidence of recurrence second in their list of recommended outcomes, immediately after the recommended primary outcome, and state that it "should be recorded as an important efficacy index"(11). Thus, migraine recurrence is an important outcome for migraine patients and it is, unfortunately, exceedingly common even after successful acute treatment of migraine in the pediatric ED.

Although migraine recurrence after pediatric ED discharge is common and is believed to have negative implications for patients and the healthcare system, there are no evidence-based treatments to prevent recurrence in this population. The literature is devoid of high quality intervention studies with a primary outcome related to migraine recurrence after pediatric ED discharge. A few studies have assessed migraine recurrence as a secondary outcome in this

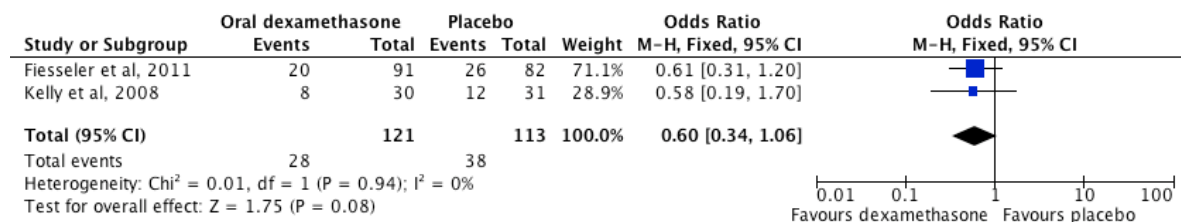
setting(8,9,12), but have failed to yield evidence for an effective therapy. Furthermore, a retrospective study in a pediatric ED failed to show an association between the specific migraine treatment administered and rates of migraine recurrence within one month of ED discharge(13). Therefore, despite the commonality of the problem, there is no evidence to guide clinicians seeking to prevent migraine recurrence after ED discharge in pediatric patients.

There is a well-established literature supporting the efficacy of steroids for the prevention of migraine recurrence in adults presenting both to outpatient settings and to the ED with migraine. A recent systematic review identified 25 studies on the efficacy of steroids for a variety of primary headache disorders in several different settings(14). The conclusion of the review was that steroids are effective for both the acute treatment of headache and for the prevention of headache recurrence. The most commonly studied steroid in the ED setting is dexamethasone. Three systematic reviews with meta-analyses(15–17) and one systematic shortcut review(18) have independently shown that dexamethasone reduces migraine recurrence in this setting. It also appears that dexamethasone is safe and well tolerated amongst adults for this indication, with dizziness being the most common symptom(15,17) and no serious adverse events reported in any of the trials(15–18). Furthermore, dexamethasone has a plausible mechanism of action in preventing migraine recurrence in that it attenuates the inflammatory response, and in some theoretical frameworks migraine is believed to be associated with neurogenic inflammation(19).

Of the thirteen dexamethasone trials carried out in the ED(20–32), two of the studies assessed the efficacy of oral dexamethasone(23,27), and the remainder randomized patients to intravenous dexamethasone. Unfortunately, neither of the studies on oral dexamethasone was powered to detect the expected minimal clinically important difference seen when comparing dexamethasone to placebo for the endpoint of migraine recurrence. The three meta-analyses that have pooled the dexamethasone studies have consistently found that dexamethasone results in a 10% lower migraine recurrence rate as compared to placebo(15–17). However, the two studies assessing oral dexamethasone selected their sample sizes based on the assumption of a 27% difference in recurrence rates(23) and a 30% difference in recurrence rates(27) when comparing dexamethasone to placebo. Thus, neither of these studies found statistically significant differences in recurrence rates, despite finding differences consistent with the pooled recurrence rates from the meta-analyses: one of the studies found that the dexamethasone group had a 10% lower recurrence rate(23) and the other found a 12% lower recurrence rate(27) for dexamethasone relative to placebo. We carried out a small meta-analysis using a Mantel-Haenszel fixed effects model in order to generate an estimate of the odds ratio and 95% confidence interval for migraine recurrence when comparing oral dexamethasone to placebo. When the results of these two small studies are pooled together, there is a trend towards significance for the efficacy of oral dexamethasone in reducing migraine

recurrence rates (OR=0.60, 95% CI: 0.34-1.06, see Figure 1). Thus, although the vast majority of the adult ED studies have assessed the efficacy of intravenous dexamethasone for the prevention of migraine recurrence, there is preliminary evidence to suggest that oral dexamethasone has the same direction and magnitude of effect for this indication.

**Figure 1. Meta-analysis on the efficacy of oral dexamethasone for the prevention of migraine recurrence in adults visiting the ED with acute migraine**



Based on the adult evidence, dexamethasone presents the most promise as a potential therapy for preventing migraine recurrence in children presenting to the ED with migraine. The proposed study intends to explore the gap in the literature regarding the treatment of migraine recurrence in the pediatric ED population. The long-term objective will be to decipher if oral dexamethasone is superior to placebo in preventing short-term migraine recurrence after ED discharge in a sample of pediatric patients visiting the ED for migraine. The proposed project aims to implement the protocol in a pilot design, which will inform the feasibility and implementation of a multi-center randomized controlled trial.

#### 4.1. Name and Description of Investigational Agent

This study will assess the efficacy and safety of oral dexamethasone for the prevention of migraine recurrence in children and adolescents visiting the ED with migraine. Dexamethasone is a synthetic glucocorticoid medication used for a variety of indications, which has anti-inflammatory action. Patients randomized to the intervention group will receive dexamethasone at a dose of 0.6mg/kg orally, for a maximum of 15mg. The oral dexamethasone solution will be compounded at CHEO from a 10mg/mL intravenous suspension prepared by Omega Laboratories Limited and an oral suspension vehicle by the name of Ora-Blend®. The suspension will have a concentration of 1mg/mL. Patients randomized to the placebo group will receive an oral solution comprised of Ora-Blend® of matched placebo at a volume of 0.6mL/mg, for a maximum of 15mL.

## **4.2. Pre-Clinical Data on Dexamethasone**

Although the pathophysiology of migraine has not been fully elucidated, it is believed that a component of migraine pathogenesis involves inflammation at the level of the meninges in the brain (33–35). There is no preclinical data specifically investigating how dexamethasone may attenuate meningeal inflammation in animal models of migraine. However, several studies have shown that dexamethasone can attenuate meningeal inflammation in the context of animal models of meningitis. In a rabbit model of meningitis, intravenous dexamethasone has been shown to attenuate lipopolysaccharide-induced inflammation in the subarachnoid space of the brain meninges by reducing tumor necrosis factor and preventing ongoing pleocytosis (36). Another study found that intravenous dexamethasone inhibited tumor necrosis factor- $\alpha$  elevations in cerebrospinal fluid after inoculation of rabbits with pneumococcal meningitis regardless of antibiotic timing (37). Other studies have found similar effects of administering dexamethasone in experimental meningitis models. For example, one study found that intravenous dexamethasone reduced brain edema in rabbits with meningitis (38). Therefore, it is known, from animal models, that dexamethasone is capable of producing a significant anti-inflammatory effect in the brain, and it is therefore possible that it may play a role in alleviating migraine or preventing recurrence of migraine given that meningeal inflammation is thought to play a role in migraine pathogenesis.

## **4.3. Known Risks and Benefits of Dexamethasone to Human Subjects**

The vast majority of the side effects reported with the use of dexamethasone are associated with chronic use as opposed to single use. The many potential adverse drug reactions associated with dexamethasone are listed in the product monograph. Possible adverse drug reactions include: hypersensitivity reaction or anaphylaxis, electrolyte disturbances, hypertension, osteoporosis, fractures, gastric or peptic ulcers, pancreatitis, esophagitis, thinning of the skin, increased susceptibility to infection, impaired wound healing, headache, convulsions, increased intracranial pressure, Cushing syndrome, menstrual irregularities, insulin resistance, adrenal suppression, growth suppression, cataracts, glaucoma, weight gain, increased appetite and psychological disturbances (see product monograph for details).

In the studies where oral dexamethasone was used to prevent the recurrence of migraine in adults visiting the ED (23,27), the following adverse events were reported in less than 10% of the patients: flushing, diarrhea, transient tingling sensations in the extremities, nausea, blurred vision and a hot sensation in the legs. In studies where intravenous dexamethasone was used to prevent the recurrence of migraine in adults visiting the ED, restlessness was reported in up

to 31% of patients(25). The following adverse events were reported in less than 25% of the patients: drowsiness(24,25), dizziness(21,24,25), nausea/vomiting(21,25,29). In these studies, the following adverse events were reported in less than 10% of the patients: acute medication reactions(24), transient tingling sensations in the extremities(20), flushing(29), insomnia(20), hiccups(20), swelling/weight gain(21), mood change(21,25), muscle cramps(21). A rash was reported by one patient in one of the intravenous dexamethasone studies(29).

Several studies have assessed the efficacy of single dose oral dexamethasone for other indications in the pediatric population. Overall, dexamethasone has been well tolerated in single oral doses in the pediatric population. Three studies did not report any significant adverse events associated with one dose of oral dexamethasone (39–41). The following adverse events have been reported in less than 10% of patients in pediatric trials of single use oral dexamethasone: vomiting(42) and abdominal pain(43). The following adverse event has been reported in less than 1% of patients in pediatric trials: pneumonia(42,44). In one study, a transient increase in blood pressure was noted, though only the average blood pressure increase was reported and the number of affected patients was not included (45). The range of doses used in these studies was between 0.15mg/kg and 1mg/kg and therefore was comparable to the dose planned for the proposed trial.

One potential idiosyncratic reaction to dexamethasone is aseptic necrosis of the femoral and/or humeral heads. This has not been reported in the ED migraine studies with single use of dexamethasone nor in the pediatric studies on single use oral dexamethasone for other indications. However, there are reports in the literature where aseptic necrosis of the femoral and/or humeral heads occurred in the context of a single dose of a corticosteroid(46,47). Although this adverse event is theoretically possible, it is exceedingly rare.

As per the product monograph (see product monograph), the use of dexamethasone in pregnancy, lactation and in women of childbearing potential has not been well studied, and a risk/benefit analysis is required prior to suggesting its use in this population. Prolonged and substantial use of steroids in pregnant women can be associated with hypoadrenalism in the infant once born (see product monograph). This is not a concern with a single and relatively small oral dose of dexamethasone.

Given the data presented above, it is anticipated that a single dose of 0.6mg/kg oral dexamethasone will be well tolerated in the pediatric migraine population.

#### **4.4. Description and Rationale for Dose, Route of Administration and Single Administration of Dexamethasone for this Indication**

The dexamethasone dosing was chosen based on both the range of dexamethasone doses administered for this indication in the adult literature, which range from 8-24mg IV(15–17), and based on the doses used in pediatric patients for other indications, which range from 0.03-2mg/kg/dose(48).

The oral route of administration was chosen based on feedback from experts. We presented this study protocol to the Pediatric Emergency Research Canada (PERC) group recently at the PERC 2015 meeting (PERC Staff Research Meetings, Banff, Alberta, February 3<sup>rd</sup> 2015). The group felt strongly that the intervention should consist of oral dexamethasone as opposed to intravenous dexamethasone. The reasons given for this penchant were two-fold: 1) there is an ongoing study at the Ste-Justine Hospital in Montreal where children are being randomized to intravenous dexamethasone vs. placebo for this indication, 2) oral dexamethasone, if proven to be effective for this indication, would benefit a greater number of patients given that many pediatric patients chose to have their migraine managed with oral therapies rather than intravenous therapies. Another reason for which dexamethasone is a promising and pragmatic intervention to study in this setting pertains to the frequency of its use for other indications in the pediatric ED. For example, clinical practice guidelines recommend the use of dexamethasone in the management of croup(49), which is a very common pediatric ED presentation. Thus, oral dexamethasone is an auspicious and pragmatic intervention to study for reducing pediatric migraine recurrence in the ED and has the potential to change practice without major barriers to its uptake.

The pharmacokinetic properties of dexamethasone in children support the rationale for using a single dose to prevent short term migraine recurrence. In children, dexamethasone has a median half life of 3.75 hours, with a reported range of 2.33 to 9.54 hours(50). In addition, it has a duration of action of up to 72 hours(48), making it plausible that it may act long enough to reduce the risk of migraine recurrence. Other pertinent pharmacokinetic properties of dexamethasone are displayed in Figure 2. This data is derived from a study carried out in twelve pediatric patients receiving intravenous dexamethasone for croup or head injury(50).

**Figure 2. Pharmacokinetic properties of dexamethasone**

**TABLE II. Dexamethasone Summary Statistics**

	$t_{1/2} (\alpha)$ (hours)	$t_{1/2} (\beta)$ (hours)	$V_D$ (steady state) (l/kg)	Average concentration ( $\mu\text{g/ml}$ )
Mean	0.86	4.34	2.07	0.142
Standard deviation	0.50	4.14	2.24	0.09
Median	0.65	3.75	1.18	0.120
Maximum	2.96	9.54	8.99	0.265
Minimum	0.18	2.33	0.48	0.053
Range	2.78	7.21	8.51	0.212
Sample size	14	14	14	14

#### **4.5. Conduct of the Trial**

The trial will be conducted in compliance with the protocol submitted to the CHEO Research Ethics. It will follow the International Conference on Harmonization Good Clinical Practice standards(51) as described in the protocol. Any protocol deviation will only be implemented after approval from the CHEO Research Ethics Board (REB), with the exception of situations where immediate implementation of a protocol deviation is necessary to protect the trial participants from hazards or where the protocol deviation is logistic or administrative in nature, in which case the CHEO REB will be notified as soon as possible.

## **5. Trial Objectives and Purpose**

### **5.1 Objectives**

To determine the feasibility of carrying out a multicenter randomized controlled trial to assess the efficacy of oral dexamethasone for preventing migraine recurrence in the pediatric ED through the implementation of a pilot randomized trial in the ED of the Children's Hospital of Eastern Ontario (CHEO). Specifically, with this pilot trial, we will aim to determine: 1) acceptability of the protocol to ED staff, 2) acceptability of the study to the participants and their families, 3) the number of patients meeting eligibility criteria, 4) recruitment rates and 5) estimates of the proportion of participants from each group who achieve the primary outcome (ie. migraine recurrence within 48 hours).

## **5.2 Primary Research Question**

To determine if oral dexamethasone is superior to placebo in preventing migraine recurrence within 48 hours of ED discharge amongst pediatric patients presenting to the ED with migraine.

## **5.3 Secondary Research Questions**

1. To determine if oral dexamethasone is superior to placebo in preventing migraine recurrence within 7 days of ED discharge amongst pediatric patients presenting to the ED with migraine.
2. To determine if oral dexamethasone is superior to placebo in preventing return ED visits within 7 days of ED discharge amongst pediatric patients presenting to the ED with migraine.
3. To determine if oral dexamethasone is superior to placebo in terms of the proportion of patients achieving persistent pain freedom 48 hours after ED discharge amongst pediatric patients presenting to the ED with migraine.
4. To determine if oral dexamethasone is associated with differential rates of patient satisfaction as compared to placebo amongst pediatric patients presenting to the ED with migraine.

## **5.4 Hypothesis**

We hypothesize that oral dexamethasone will be superior to placebo in preventing migraine recurrence within 48 hours of ED discharge amongst pediatric patients presenting to the ED with migraine. It is anticipated that oral dexamethasone will be safe, well tolerated and simple to use for this indication.

# **6. Eligibility Criteria**

## **6.1. Inclusion Criteria**

Patients will be eligible for the study if:

1. Between the ages of 8 and 18 years (ie. > 8.0 years and < 18.0 years)
2. Diagnosed with migraine according to a modified version of International Classification of Headache Disorders 3<sup>rd</sup> edition (ICHD-3, beta version, see Table 1) diagnostic criteria for pediatric migraine(52)

NB. The use of the International Classification of Headache Disorders for migraine diagnosis is the standard for trials assessing both acute and prophylactic medications for migraine, according to the 2012 International Headache Society guidelines for controlled trials of drugs in migraine (3<sup>rd</sup>



edition)(11). However, there has been controversy about the application of these criteria to trials in the ED and many ED trials have used other criteria for migraine diagnosis. Both an adult(53) and a pediatric study(54) have shown that the ICHD criteria lack sensitivity for migraine diagnosis in the ED. Criterion A, which establishes that patients must have had five headaches meeting ICHD migraine criteria, is particularly problematic in the ED setting for several reasons, one of which is that patients commonly present to the ED with their first migraine and will therefore not meet this criterion. It has been shown that removal of criterion A increases the sensitivity of the ICHD criteria in the ED setting(54,55). Hence, for the proposed study, criterion A will be modified to increase the sensitivity of the criteria: criterion A will only require that the current headache meet ICHD-3 (beta) criteria, as opposed the requirement for five headaches meeting criteria (see Table 1).

**Table 1. International Classification of Headache Disorders 3<sup>rd</sup> edition (beta version) criteria for pediatric migraine(52) and modified criteria for proposed study**

<b>Criterion</b>	<b>ICHD-3 (beta) Migraine Criteria</b>	<b>Modified Criteria for Proposed Study</b>
<b>A</b>	At least 5 attacks fulfilling criteria B-D	Present attack fulfilling criteria B-D
<b>B</b>	Attacks last 2-72 hours if untreated or unsuccessfully treated	<ul style="list-style-type: none"> <li>Attack lasting 2-72 hours if untreated or unsuccessfully treated</li> </ul>
<b>C</b>	At least 2 of the following 4 characteristics are present: <ul style="list-style-type: none"> <li>Unilateral or bilateral in children and adolescents, most often frontotemporal</li> <li>Pulsating quality</li> <li>Moderate or severe pain intensity</li> <li>Aggravated by or causing avoidance of routine physical activity such as walking or climbing stairs</li> </ul>	At least 2 of the following 4 characteristics are present: <ul style="list-style-type: none"> <li>Unilateral or bilateral in children and adolescents, most often frontotemporal</li> <li>Pulsating quality</li> <li>Moderate or severe pain intensity</li> <li>Aggravated by or causing avoidance of routine physical activity such as walking or climbing stairs</li> </ul>
<b>D</b>	At least one of the following is present: <ol style="list-style-type: none"> <li>Nausea and/or vomiting</li> <li>Photophobia and phonophobia</li> </ol>	At least one of the following is present: <ol style="list-style-type: none"> <li>Nausea and/or vomiting</li> <li>Photophobia and phonophobia</li> </ol>
<b>E</b>	Not better accounted for by another ICHD-3 diagnosis	Not better accounted for by another ICHD-3 diagnosis

## 6.2 Exclusion Criteria

Patients will be excluded for the following reasons:

1. Received a dose of a steroid medication in the past 7 days
2. Known allergy to dexamethasone
3. Immunosuppressed

4. Cushing's syndrome
5. Known diabetes mellitus
6. Known peptic or duodenal ulcer or other major gastrointestinal illness (ex. ulcerative colitis)
7. Known myasthenia gravis
8. Glaucoma
9. Febrile at triage
10. History of head trauma in the past 7 days
11. Presence of any known active infection (eg. on antibiotics or antivirals, diagnosed with active infection in the ED, etc)
12. Current secondary headache (as per the treating physician's clinical impression)

## **7. Study Design**

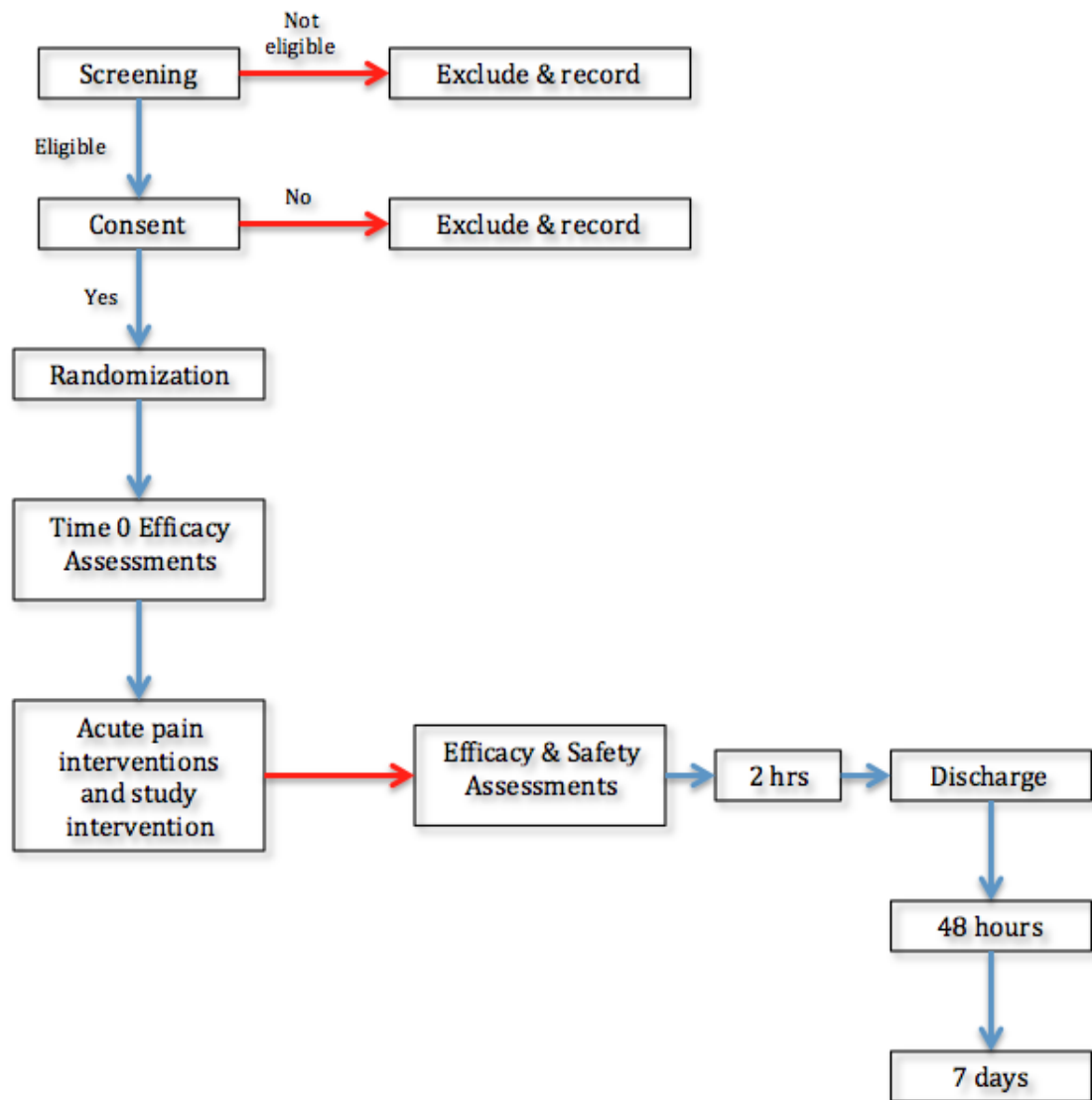
### **7.1. Description**

The proposed study will be a Phase III pilot trial, designed as a 2-arm, parallel-group, randomized, placebo-controlled, double-blind study.

### **7.2 Description of the Study Stages**

Twenty children and adolescents will be enrolled into this trial. The expected duration of the study will vary from patient-to-patient based on how many interventions for acute migraine pain will be administered, and these decisions will be made at the discretion of the treating physician. On average, it is expected that the duration of study participation in the ED will vary between 2 and 6 hours. There will be either a telephone follow-up with a research assistant approximately 48 hours after discharge and then a second telephone follow-up 7 days after discharge, or an email follow-up at 48 hours and 7 days with electronic questionnaires sent directly to participants, depending on participant preference.

**Figure 3. Study Flow Diagram**



### 7.3 Screening

Patients presenting to the CHEO ED with a triage diagnosis of headache, migraine or a related term (eg. head pain) who are interested in discussing the study will be screened for eligibility by SUPPORT (Students Undertaking a Pediatric Program of Research Training) volunteers. The SUPPORT program is a specialized volunteer program at CHEO that trains volunteers to assist in recruiting patients to clinical studies based in the ED. Prior to approaching potentially eligible patients, the SUPPORT volunteer will ask the patient if they are willing to discuss the study with them. Should a patient agree, the SUPPORT

volunteer will introduce the patient and their family to the study and if they are interested, they will carry out the eligibility screening (see Appendix A for screening questionnaire). If a participant is deemed eligible from the screening questionnaire administered by the SUPPORT volunteer, the volunteer will first ask the treating physician to verbally confirm that they agree with the diagnosis of migraine and that secondary headache is not present, and if the physician agrees, the volunteer will then notify the research assistant about the potential participant.

The research assistant will then meet with the potential participant to initiate the consent process. For patients over the age of 16, verbal and written consent will be sought from patients and their parent or guardian by the study assistant. For patients under the age of 16, verbal and written assent will be sought from the patient, and verbal and written consent will be sought from the parent or guardian. Study packages including consent forms, informational brochures and pre-printed orders for enrolled participants will be stored in the ED. There will be three sets of packages, one for each stratum, and the packages will be pre-labeled with a numeric randomization code from the randomization scheme which will also serve as the participant identification number.

The Maternal, Infant, Child and Youth Research Network (MICYRN) tool, an instance of Research Electronic Data Capture (REDCap)(56), is a secure, web-based, encrypted application and will be used for screening potentially eligible participants and for all data entry for enrolled participants. Basic demographic characteristics of patients who were screened for enrollment and who were ultimately excluded will also be recorded in MICYRN by the SUPPORT volunteers, along with the reason for exclusion (eg. declined, ineligible, etc; see Appendix B). The demographic characteristics that will be recorded for excluded patients will be the following: sex, age, Canadian Triage and Acuity Scale (CTAS) score and time of presentation (time of day) (see Appendix B).

**Table 2. Study Schedule**

Procedure	Screening	Baseline	Randomization/ Treatment	2 hours	Discharge	48 hour follow up	7 day follow up
Recording of reasons for refusal, missed enrollment, etc	x						
Assessment of eligibility criteria	x						
Contact information		x					
Vital signs		x					
Demographics and migraine history		x					
Physical exam		x					
Urine pregnancy test (where applicable)		x					
Pharmacy carries out randomization			x				
Dispense study intervention			x				
Assessment of pain intensity		x		x	x	x	x
Assessment of patient satisfaction				x	x	x	x
Assessment of missed time at work or school						x	x
Assessment of adverse events				x	x	x	x
Assessment of headache recurrence						x	x

## 7.4 Randomization

Patients consenting to participation and meeting eligibility criteria will be randomly assigned to receive either dexamethasone or placebo in a 1:1 ratio. Prior to randomization, the research assistants will ensure that the baseline assessment is complete (see case report form in Appendix C) and that contact information is collected for the purposes of follow-up (see paper-based contact information form in Appendix D). Randomization will be stratified according to the length of current migraine duration (less than 2 hours,  $\geq 2$  and  $< 24$  hours or  $\geq 24$  hours). Within each stratum, randomization will be blocked in blocks of four. A statistician will create the randomization scheme. The statistician will generate a list of random numbers for each stratum that will correspond to

specific group assignments. Group assignment will be encoded using a digit numeric coding system rather than a dichotomous group A or B system to better ensure blinding. The list will be sent to the research pharmacy and will not be accessible to anyone involved with the study outside of the pharmacy. The allocation will remain concealed to all study participants, study personnel and clinical staff.

The research pharmacists will maintain a password-protected list of the patients' names, their assigned numeric codes, their hospital identification numbers and their group allocations. Only the research pharmacists will have access to the list linking the assigned numeric code and group allocation to the patient's name and identifying information. In addition, the data safety monitoring board, or, where necessary, clinical staff or study investigators, will be given access to specific pertinent data from the list if safety issues or adverse events occur.

## **7.5 Baseline Assessment**

The baseline assessment will involve a physical exam, which will be carried out by the ED physician as part of routine clinical care. After eligibility screening, the SUPPORT volunteers will confirm with the physician that a physical exam was done and that secondary headache was ruled out on physical exam. At this time, should the SUPPORT volunteer have any concerns about exclusion criteria (eg. presence of active infection) that were not resolved after talking to the patient and family, they can also ask the ED physician about their opinion regarding exclusion criteria given data acquired from the physician's history and physical exam.

In addition to the physical exam, the research assistant will take a targeted migraine history, record the patient's past medical history, record the vital signs from the chart and identify the baseline pain level of the patient using a 4-point scale where 0=no headache, 1=mild headache, 2=moderate headache and 3=severe headache (see Appendix C). The headache history will include questions pertaining to migraine diagnosis, presence of aura, headache duration, headache frequency, headache intensity, baseline migraine-related disability as measured by the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire (see Appendices C and E), and treatment of the headache prior to presentation to the ED (see Appendix C). The four point pain rating scale is being used in accordance with the recommendation set out in the International Headache Society guidelines for controlled trials of drugs in migraine(11).

## **7.6 Study Intervention Administration and Efficacy Assessments**

Once the baseline assessment is completed, the study intervention will be administered. Acute pain interventions will also be administered at the discretion of the treating physician. Pre-printed orders will be prepared by the research pharmacy in order to simplify study procedures and prevent errors. The pre-printed orders will be stored in study packages along with the consent forms and the informational brochures (see Appendix F). Three sets of study packages will be stored in the ED: one for each randomization stratum. The study intervention will be administered by the treating nurse.

A research assistant will assess pain 2 hours post-intervention and at the time of discharge, using the 4-point rating scale described above. Should the patient be discharged prior to the 2 hour post-intervention time point, the discharge pain assessment will replace the 2 hour post-intervention assessment. At the time of discharge, patient satisfaction will also be assessed by the research assistant, using a 5-point Likert scale where 5=very satisfied, 4=satisfied, 3=neutral, 2=unsatisfied, 1=very unsatisfied. In the event where a participant is discharged prior to having an efficacy assessment by the research assistant, an electronic questionnaire will be sent to the participant as a proxy for the in-person ED discharge assessment. If adverse events are reported on the electronic questionnaire, then the participant will be called to further assess the adverse event(s).

## **7.7. Follow-Up**

In the ED, study participants will receive a brochure (see Appendix F) about the study from the research assistant at the time of enrollment. The brochure will briefly describe the aims of the study, and will detail the timing and options for follow-up.

Participants will be offered the option of completing their follow-up via a self-administered electronic questionnaire sent through MICYRN, or over the phone with a research assistant. If they chose the option of the self-administered electronic questionnaire, they will receive an email with a link to the MICYRN-based questionnaire at 48 hours and 7 days post-intervention. Should they not complete the given questionnaire within 24 hours of their first notification, a second email will be sent. Should they fail to complete the given questionnaire within 24 hours of the second notification, the research assistant will contact them over the telephone for the given follow-up.

For participants selecting the option of telephone follow-up, the research assistant will call the patient for a follow-up telephone-administered questionnaire approximately 48 hours after discharge and 7 days after discharge (see Appendix C). In the event where it is not possible to contact a patient for follow-up over the telephone after several attempts, follow-up

questionnaires will be emailed to the participant through MICYRN with 24 hours reminders as above.

When an adverse event is reported during follow-up on one of the electronic questionnaires, the participant will be contacted over the telephone in order to clarify details pertaining to the adverse event.

Participants who complete both follow-up questionnaires will be sent electronic gift cards for Chapters Indigo in the amount of 10\$ via email.

## **7.8. Chart Review**

The research assistant will review the chart 7 days after admission or later in order to record any return visits to the ED. Return visits will be coded as either headache-related or unrelated (see CRF in Appendix C).

## **7.9. Study Endpoints**

### ***7.8.1 Primary Outcome***

The primary outcome will be headache recurrence 48 hours after discharge. Headache recurrence will be defined as: for patients who were pain-free at ED discharge (ie. pain intensity of 0), any return of head pain (ie. pain intensity of 1 or greater) will be coded as a recurrence, and for patients who had persistent head pain at discharge, an increase in head pain since ED discharge will be coded as recurrence as well (ie. an increase in their score on the 4-point scale as compared to their score at ED discharge). Therefore, the primary outcome will involve the comparison of the proportion of patients with headache recurrence in each group within 48 hours of ED discharge. Although formal statistics on reliability and validity are unavailable, assessment of the primary outcome, as described above, is congruent with prior studies on the efficacy of dexamethasone for this indication in adults(24,29).

The rationale for using headache recurrence as the primary outcome is derived from evidence from adult studies that have established efficacy for dexamethasone in preventing migraine recurrence in the short-term(15–18), but found no apparent impact on acute pain relief in the ED setting(57). The rationale for measuring recurrence of headache at 48 hours is three-fold: 1) the International Headache Society guidelines for controlled trials of drugs in migraine(11) defines recurrence as “any headache pain from 2 to 48 hours after drug administration, regardless of its severity”, 2) prior studies assessed the efficacy of steroids (including dexamethasone) in preventing migraine recurrence anywhere from 24 to 72 hours after treatment, with the 48 hour mark being used most commonly(20,22,24–26,29,58–60), 3) the half-life of dexamethasone in children and adolescents is somewhere between 2.33 and 9.54 hours(50), meaning that it is cleared from the body between 11.7 and 47.7



hours after ingestion (after 5 half-lives only 3.1% of the drug remains in the body).

### **7.8.2 Secondary Outcomes**

Several secondary outcomes are of interest:

1. Pain intensity will be assessed at baseline, 2 hours after having received the study intervention (or at the time of ED discharge if prior to 2 hours) and at the time of ED discharge. As is suggested in the International Headache Society guidelines for controlled trials of drugs in migraine(11), pain intensity will be measured using a 4-point scale where 0=no headache, 1=mild headache, 2=moderate headache and 3=severe headache.
2. Persistent pain freedom, defined as the proportion of patients in each group who achieved pain freedom at 2 hours (or at the time of ED discharge if prior to 2 hours) and were free of pain without the use of rescue medication at 48 hours(11), will be assessed.
3. Patient satisfaction will be assessed at discharge and again at follow-up with the following 5-point Likert scale: 5=very satisfied, 4=satisfied, 3=neutral, 2=unsatisfied, 1=very unsatisfied.
4. The proportion of patients in each group with recurrence within the 7 days following ED discharge will be assessed. The 7 day time point was selected based on its use in a previous study(29) and given our interest in exploring potential longer treatment effects of dexamethasone for this indication.
5. The number of patients with return ED visits within 7 days of ED discharge will be assessed through chart review.
6. Adverse events will also be queried at 2 hours (or at the time of ED discharge if prior to 2 hours), at discharge and in the follow-up questionnaires.

## **8. Expected Duration of Participant Participation**

Participants will remain in the ED for variable lengths of time depending on the time required for the acute pain interventions to alleviate the migraine pain. It is anticipated that participants will remain in the ED for 1.5-6 hours on average. Participants will also be asked to complete two electronic or telephone follow-up questionnaires, which are expected to last a maximum of 5 minutes per follow-up. Participation in the study will end after the second follow-up electronic or telephone questionnaire, that is, 7 days following discharge.

## 9. Study Medication

### 9.1 Study Medication Description

The study intervention will consist of an oral compound of dexamethasone, given orally at a one time dose of 0.6mg/kg to a maximum of 15mg. The dexamethasone will be compounded at the CHEO research pharmacy using a combination of dexamethasone sodium phosphate USP injection 10mg/mL (<sup>PR</sup>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. The commercial label will not be present given that this study is blinded.

### 9.2 Placebo Description

The placebo will comprise Ora-Blend®, a flavored oral suspending vehicle manufactured by Galenova Inc. Participants randomized to the placebo group will be given Ora-Blend® 0.6mL/kg for a maximum of 15mL. Ora-Blend® has a pinkish hue and a milky consistency. The appropriate volume for the participant will be drawn up into an oral syringe, which will be labeled for investigational use. The commercial label will not be present given that this study is blinded.

### 9.3 Accountability Procedures and Storing

The dexamethasone oral suspension will be stored in the Pharmacy Department in amber plastic bottles at room temperature, between 20°C and 25°C. The Ora-Blend placebo suspension will also be stored in the Pharmacy Department, in white opaque bottles at room temperature, between 20°C and 25°C. The compound maintains stability for 91 days(61,62) and the vials will be labeled with the expiration date. After the expiration date, remaining vials will be destroyed in compliance with the Pharmacy Department's standard operating procedures (SOP) for the destruction of investigational drugs, which are compliant with the guidelines as set out in ICH(51).

The dexamethasone and placebo vial labeling will be compliant with Health Canada Division 5 Food and Drug Regulation clinical trial labeling guidelines (see Figures 4 and 5 for labels).

**Figure 4. Labels for dexamethasone vials**

Dexamethasone 1mg/mL oral suspension- X mL Expiration: DD-MMM-YYYY Store at room temperature +20°C and +25°C, protected from light in amber plastic bottles Lot # ----- Protocol Code: ----- Sponsor: Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1 Investigational drug to be used only by a qualified Investigator	Dexamethasone Suspension 1mg/mL orale- X mL Expiration: DD-MM-YYYY Conserver à température ambiante entre +20°C and +25°C, à l'abri de la lumière dans des bouteilles en plastique couleur ambre et opaques Lot # ----- Code du Protocole: ----- Commendaire: Centre Hospitalier Pour Enfants de L'Est de L'Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1 Médicament expérimental à être utilisé seulement par un Investigateur qualifié
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**Figure 5. Labels for placebo vials**

Placebo (Ora-Blend®) 1mg/mL oral suspension- X mL Expiration: DD-MMM-YYYY Store at room temperature +20°C and +25°C, protected from light in white opaque bottles Lot # ----- Protocol Code: ----- Sponsor: Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1 Investigational drug to be used only by a qualified Investigator	Placebo (Ora-Blend®) Suspension 1mg/mL orale Expiration: DD-MM-YYYY Conserver à température ambiante entre +20°C and +25°C, à l'abri de la lumière dans des bouteilles blanches et opaques Lot # ----- Code du Protocole: ----- Commendaire: Centre Hospitalier Pour Enfants de L'Est de L'Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1 Médicament expérimental à être utilisé seulement par un Investigateur qualifié
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When a patient is randomized to the study, pre-printed orders with the participant's identification number (corresponding to the randomization code, see above), and their identifying information (ie. name, hospital identification number, etc) will be sent to the Pharmacy. The research pharmacist will then check the randomization scheme and prepare the appropriate intervention, either dexamethasone or placebo, according to the participant's identification number/randomization code. At this time, the patient's identifying information will be entered into the research pharmacy's password-protected group assignment list along with their study identification number and assigned intervention, so that this data is recorded in case unblinding is required for safety reasons.

The study intervention will be drawn into a syringe, which will be capped and labeled in compliance with Health Canada Division 5 Food and Drug Regulation clinical trial labeling guidelines and the guidelines of the Ontario College of Pharmacists. Once the syringe is filled, capped, and labeled, a research pharmacist or technologist will bring it to the ED and deliver it to the treating nurse.

Syringes that are not administered to patients will be sent back to the Pharmacy Department for destruction according to the Pharmacy's SOPs for destruction of investigational products.

Drug accountability forms will be completed and stored in the Pharmacy and records will be maintained in accordance with Health Canada Division 5 Food and Drug Regulation guidelines.

#### **9.4 Monitoring for Subject Compliance**

Given that this study will involve a one time oral dose of either dexamethasone or placebo given in the ED, no compliance issues are anticipated. Loss to follow-up will likely occur. Given that this is a pilot randomized controlled trial, monitoring of the rate of loss to follow-up is one of the goals of the study.

## **10. Statistical Procedures**

### **10.1 Sample Size**

As described above, the proposed study will be a pilot study. The goal will eventually be to use this pilot data to inform the design and implementation of a large, multi-center trial on the efficacy of dexamethasone for preventing migraine recurrence in the pediatric ED. For the purposes of the proposed pilot study, 20 patients will be recruited. The recruitment period will be over 6 months. The CHEO ED has over 300 migraine visits per year, and 6 months is thus expected to be a sufficiently long period to capture 20 eligible migraine patients.

### **10.2 Outcome Analysis Plan**

Demographic characteristics for each group will be presented descriptively in tabular form. The primary outcome pertains to comparing the proportion of patients in each group with headache recurrence. Because of the small sample size, we will use a Fisher's exact test to compare the two groups on the primary outcome. A two-sided p-value less than 0.05 will be considered statistically significant. The relative risk of headache recurrence, together with a 95% confidence interval, will be computed.

The secondary outcomes will be analyzed in the same fashion as the primary outcome. The proportion of migraine recurrence at 7 days, the proportion of patients with return ED visits and the proportion of patients who achieve persistent pain freedom at 48 hours are all binary outcomes where the interest lies in comparing proportions between the two groups. The patient satisfaction outcome is an ordinal categorical variable with five possible responses graded on a Likert scale (see Appendix C). We will dichotomize this variable into two possible outcomes: 1) satisfied (coded as 1), where the sum of the frequencies for 'very satisfied' and

'satisfied' will be added together, 2) not satisfied (coded as 0), where the sum of the frequencies for 'neutral', 'unsatisfied' and 'very unsatisfied' will be added. Again, due to the small sample size, we will use a Fisher's exact test to compare the proportions between the groups for each secondary outcome.

Adverse events will be presented descriptively in tabular form, with the frequency and percentage of each adverse event listed by the corresponding group.

## 11. Safety and Adverse Events

### 11.1 Safety Assessments

As is described above, few adverse events are anticipated with single use of oral dexamethasone. The following are potential adverse events that could occur from single use of dexamethasone, as has been reported in the adult migraine literature as well as the pediatric literature where oral dexamethasone was used as a one time dose for other indications:

- Abdominal pain: In one pediatric study on single use oral dexamethasone in the pediatric population, 3.5% of patients reported abdominal pain. Should a patient experience significant abdominal pain after the administration of dexamethasone, the treating physician will administer analgesics at his or her discretion.
- Anaphylaxis/hypersensitivity reaction: Hypersensitivity reactions and anaphylaxis are listed as possible adverse drug reactions in the product monograph. In one of the adult intravenous dexamethasone studies, acute medication reactions occurred in less than 10% of the patients(24), and in one study a patient reported a rash(29). As per the product monograph, patients with anaphylaxis to dexamethasone will be managed in the ED with close monitoring of vital signs, airway support where required, appropriate doses of epinephrine and aminophylline if needed. Patients with hypersensitivity reactions will be closely monitored in the ED until the treating physician deems that discharge is safe. Treatment for hypersensitivity reactions will depend on the nature and severity of the reaction and will be administered at the discretion of the treating physician.
- Aseptic necrosis of the femoral and/or humeral head: Limited case reports have identified the possibility of aseptic necrosis of the femoral and/or humeral head following single doses of corticosteroids(46,47). Although this adverse event is exceedingly rare with single doses of corticosteroids, any patient reporting hip or shoulder pain in the ED will have anteroposterior and frog-leg radiographs of the hip(63) and/or shoulder radiographs to screen for aseptic necrosis of the affected joint. Should the radiographs not

reveal evidence of aseptic necrosis, an MRI will be pursued(63). Patients reporting the new onset of shoulder or hip pain during telephone follow-up will be instructed to return to the ED for an assessment. Patients with evidence of avascular necrosis will be urgently referred to Orthopedics for management.

- Blood pressure increase: Although blood pressure increase has been reported in one study on single use oral dexamethasone in the pediatric population, this increase did not require treatment and was clinically insignificant, with an average change in systolic blood pressure from 96.1mmHg  $\pm$  8.8mmHg to 99.5mmHg  $\pm$  14.8mmHg(45). We therefore do not anticipate that changes in blood pressure will constitute clinically significant events in our proposed study.
- Blurred vision: One adult patient reported blurred vision following a one time dose of oral dexamethasone in one of the randomized controlled trials(27). Although we do not anticipate that this will occur in our population, if a patient reports blurred vision while in the ED, the treating physician will reassess the patient and determine a plan of action. Should a patient report blurred vision during telephone follow-up, that patient will be instructed to return to the ED for an assessment.
- Diarrhea: Amongst the studies on single use oral dexamethasone reviewed, only one adult patient reported diarrhea in this context(27). If significant diarrhea occurs amongst one of the study patients, instructions will be given to the patient to return to the ED for an assessment.
- Drowsiness: In two of the adult intravenous dexamethasone studies, drowsiness was reported in under 25% of participants(24,25). Should a patient report drowsiness persisting beyond 24 hours, they will be instructed to discuss the symptom with their primary care provider or to return to the ED if the drowsiness is impairing or severe.
- Facial flushing: One adult patient given a single oral dose of dexamethasone to prevent migraine recurrence reported facial flushing(27). Although this will be recorded as an adverse event, it is a transient phenomenon that is not associated with any harm to the patient and does not require specific treatment.
- Hiccups: In one adult study of intravenous dexamethasone, hiccups were reported in one participant(20). This is expected to be a self-limited symptom. If hiccups persist or are disruptive to the participant, they will be asked to follow-up with their primary care provider.

- Muscle cramps: In one of the adult studies on intravenous dexamethasone in adults, one participant reported muscle cramps(21). Because muscle cramps may indicate an underlying electrolyte imbalance which is an adverse drug reaction reported in the product monograph, participants experiencing muscle cramps persisting beyond 7 days of discharge or which are continuous for more than 24 hours will be asked to return to the ED for an assessment.
- Nausea: Nausea does not appear to be a common side effect with single use oral dexamethasone, as it was reported by one adult in the studies reviewed. Should nausea occur in the ED setting, the treating physician will discuss treatment options with the patient. Should nausea occur after discharge and be reported in the telephone follow-ups, the patient will be instructed to return to the ED if symptoms are not responding to therapies at home.
- Pneumonia: In two of the pediatric studies, one where dexamethasone was given for croup(44) and the other where it was given for bronchiolitis(42), pneumonia was reported in less than 1% of patients. Although it is not anticipated that pneumonia will occur in our patient population, should any new respiratory symptoms or fever develop in the days following administration as reported on telephone follow-up, then patients will be instructed to return to the ED for a visit.
- Psychic derangements: Psychic derangements are listed as possible adverse drug reactions in the product monograph and have been reported in some of the studies reviewed. These include insomnia(20), mood changes (21,25), a feeling of restlessness(25), depression and euphoria. These derangements are expected to be self-limited if they occur. Participants reporting any of these symptoms will be instructed to discuss the symptom with their primary care provider if it persists for more than a week and is bothersome. In the case of severe psychic derangements (eg. severe depression with suicidal ideation), the participant will be instructed to return immediately to the ED.
- Swelling/weight gain: In one of the adult intravenous dexamethasone studies, less than 5% of participants reported swelling/weight gain(21). Weight gain is also listed in the product monograph in possible adverse drug reactions (see product monograph). Should a patient experience weight gain, they will be asked to follow-up with the primary care provider, unless the degree of weight gain is excessive in a short time frame indicating the need to have a more urgent assessment. Because significant weight gain may indicate an underlying electrolyte imbalance which is an adverse drug reaction reported in the product monograph, participants gaining more than 5% of their body weight within a week of discharge will be asked to return to the ED for an assessment.

- Unusual sensations in the extremities: Two adults have reported transient tingling sensations in the hands or feet in one of the adult studies or oral dexamethasone(27) and one adult reported a “hot sensation in the legs”.. Should this type of symptom occur while a patient is in the ED, the treating physician will reassess the patient. Should a patient report this type of symptom at follow-up, they will be instructed to discuss the symptom with their primary care provider if it persists for more than 24 hours.
- Vomiting: In one of the pediatric studies, 5.5% of the patients receiving dexamethasone reported vomiting within 20 minutes of the administration of oral dexamethasone(42). Should this occur in our population, the treating physician will reassess the patient for management of vomiting and hydration status. Management changes will be at the discretion of the treating physician.

## **11.2 Methods and Timing of Safety Assessments and Follow-Up**

As is described above, assessment of adverse events will occur during the ED visit at 2 hours post-intervention (or at the time of ED discharge if prior to 2 hours) and at discharge. During the 48 hour and 7 day electronic or telephone follow-ups, participants will again be asked if any adverse events have occurred. In the events where a participant indicates that an adverse event has occurred, they will be asked to describe those adverse events either in written form (for those completing electronic questionnaires) or verbally (for those completing telephone questionnaires). Participants completing electronic questionnaires and endorsing adverse events at follow-up will also be contacted over the telephone to clarify the nature of the adverse events. The Qualified Investigator or co-investigator will assess the potential relatedness of each AE to the investigational product during the trial.

All participants experiencing adverse events in the ED will be contacted over the telephone for follow-up (as opposed to being offered the option of electronic follow-up). Follow-up of adverse events occurring in the ED will also occur during the 48 hour and 7 day telephone follow-ups. In instances where the adverse event is first reported at the 7 day follow-up, an additional telephone follow-up 48 hours after the 7 day follow-up will be scheduled.

Although general follow-up timeframes are described above, extended follow-up will occur as required when the event does not resolve or stabilize within the above timeframes and the frequency, nature and timing of the extended follow-up will be determined by the Qualified Investigator. In addition, the Qualified Investigator may choose to schedule in-person follow-up in lieu of telephone follow-up when deemed necessary for participant safety.



### 11.3 Definitions Pertaining to Adverse Events

Adverse events (AEs) will be reported from the time the informed consent is obtained until the subject completes the last study procedure.

We will define AEs in accordance with the definitions set out by the International Conference on Harmonization (ICH E2A topic) and the CHEO REB SOP #REB-005:

Adverse event: Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Adverse drug reaction: Any response to a drug, biologic, or natural health product which is noxious and unintended, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function. A reaction, as opposed to an adverse event, is characterized by the fact that a causal relationship between the product and the occurrence is suspected (i.e. judged to be at least a reasonably possibility).

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Unexpected adverse drug reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Unanticipated problem: Any incident, experience, or that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the REB-approved research protocol and informed consent document, or the

- Investigator Brochure; and (b) the characteristics of the research participant population being studied; and
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the [investigational product(s)] or procedures involved in the research); and
  - Suggests that the research places research participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious adverse event: Adverse events will be classified as serious or non-serious. A serious adverse event is defined as any AE that is:

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

The **severity** of an adverse event will be determined by the investigator, who should use the following definitions when assessing the intensity of an adverse event:

1. MILD: Participant is aware of symptoms or has minor findings but tolerates them well and no or minimal intervention required
2. MODERATE: Participant experiences enough symptoms or findings to require intervention
3. SEVERE: Participant experiences symptoms or findings that require significant intervention

An event will be qualified as **unexpected** when the specificity or severity of the event is not consistent with the package inserts or investigational brochure for the drugs under study.

**Causality** will be determined by the following question, where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the drug caused the event? “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the specific adverse event being assessed.

In relation to the **identification of adverse events**, some participants in this study will have pre-existing medical conditions and those pre-existing conditions will not be considered as adverse events. New events that occur or the worsening in frequency or intensity of pre-existing conditions will be reported as adverse events (Schedule of Events). All reportable events as defined above, determined to be an AE based on physical examination, laboratory findings, or other means will be

recorded in the source documents and entered in the CRF. Each event will be recorded on an AE CRF starting after first dose of study drug has been delivered. The investigator will provide date of onset and resolution, severity, action(s) taken, changes in study drug dosing, causality to study drug, and outcome.

For **follow-up of AEs**, any safety event that is identified at the last assessment (or an early termination) will be recorded on the CRF with the status of the safety event noted. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the patient is medically stable.

## 11.4 Recording and Reporting of Adverse Events

All adverse events, adverse drug reactions and unanticipated problems will be recorded on the electronic adverse event form (see Appendix G), which will be stored in MICYRN.

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

During this trial, the sponsor (The Children's Hospital of Eastern Ontario) will inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:

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

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

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

Final reports of fatal or life-threatening reactions will include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

In addition to the above, if any additional situations arise, appropriate scientific and medical judgment will be applied to determine if rapid communication to Health Canada is required. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations where rapid communication to Health Canada will occur; including:

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

As per the ICH Good Clinical Practice Guidelines stipulations, the Children's Hospital of Eastern Ontario Research Ethics Boards will establish, document in writing and follow procedures for:

- Determining the frequency of continuing review as appropriate (including adverse drug reactions and adverse events) and
- Requiring that the **Investigator** should promptly report to the REB
  - Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial;
  - All adverse drug reactions that are both serious and unexpected
  - New information may affect adversely, the safety of the subjects or the conduct of the trial.

In additions to the reporting to Health Canada as described above, all serious adverse events that occur at CHEO along with any adverse events that are both serious and unexpected, will be reported to the CHEO Research Ethics Board.

## **11.5 Treatment Discontinuation**

Although this is a one time dose of oral dexamethasone, participants can decide to withdraw from the study at any time point. Participants withdrawing from the study will continue with the planned study follow-ups if they provide permission for ongoing follow-up.

## **11.6 Premature Study Discontinuation for Individual Participants**

A participant will be permanently discontinued from the study when:

- Consent is withdrawn by the participant (ie. the participant requests to discontinue the trial)
- The investigator believe that ongoing participation in the trial will either pose a significant risk to the participant, invalidate the results of the study or involve a high risk of self-harm
- Loss to follow-up involving absence of all efficacy assessments and follow-up assessments for any reason

## **11.7 Protocol Deviations and Violations**

A protocol deviation is defined as any modification or alteration of the REB approved protocol. A major deviation is defined as a modification or alteration of the REB approved protocol involving a potential impact on the participants' safety, rights, welfare or a potential impact on the integrity of the data. A minor deviation is defined as a modification or alteration of the REB approved protocol involving no significant impact on the study.

No deviations from the protocol will occur prior to having received written permission from the CHEO REB, except where required to protect participants from hazards or where the deviation is limited to a logistical or administrative aspect of the trial. In such instances, the REB will be notified as soon as possible about the deviation.

## **12. Data Handling and Record Keeping**

### **12.1 Data Collection**

All data in the ED will be collected by the research assistants. Follow-up data will either be self-reported through electronic questionnaires for participants selecting this option, or will be captured over the telephone by the research assistants. The participants and research assistants will remain blinded to group assignment and will assess and report all outcomes. Data will be inputted directly into an electronic CRF on the MICYRN instance of the Research Electronic Data Capture (REDCap)(56) application (see Appendix C).

REDCap is a secure, web-based application hosted by the Women's and Children's Health Research Institute's Clinical Research Informatics Core that is compliant with ICH Good Clinical Practice Guidelines section 5.5.3. REDCap is designed for the purposes of capturing data 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.

The Maternal Infant Child Youth Research Network (MICYRN), a network of academic health centres, was founded in 2006 as a collaborative national initiative to build capacity for high quality clinical research in Canada. Recognizing the need to establish and support standards in clinical research MICYRN has adopted the REDCap application to provide a shared data capture platform. The application is installed in a secure data centre provided by the Faculty of Medicine and Dentistry at the University of Alberta. It is managed and supported by the Women and Children's Health Research Institute's Clinical Research Informatics Core. The application has been validated by MICYRN members and is operated according to established standard operating procedures.

## **12.2 Confidentiality**

All participant information will be kept strictly confidential. The only paper-based forms that will be completed for the purposes of this study will be the consent form and the Participant Contact Information Form (see Appendix D). The paper-based forms will be kept separate from all other study data, in a locked, secure location. Study data will be entered into an electronic data capture system, MICYRN, as described above. Data entered into MICYRN will be de-identified and coded using a numeric code only. The electronic data in MICYRN will be encrypted and password-protected.

Upon request, participant records will be made available to the sponsor (the CHEO Research Institute), Health Canada or other applicable regulatory agencies.

## **12.3 Record Retention**

Study records will be retained for 25 years in accordance with Division 5 of Health Canada's Food and Drug Regulations.

# **13. Quality Control and Quality Assurance**

## **13.1 Study Monitoring Plan**

The study will comply with the ICH Good Clinical Practice Guidelines, the requirements of the CHEO REB and Division 5 of Health Canada's Food and Drug Regulations.

A study binder detailing all standard operating procedures and including a copy of the protocol will be kept on site and accessible to all research personnel. Prior to trial commencement, the site investigators will give a presentation to the research personnel outlining the study protocol, documentation and reporting procedures. In

order to keep ED physicians informed about the study and engaged, the site investigators will also carry out a presentation at the CHEO ED grand rounds in the weeks leading up to study initiation to present the purposes of the study, its design and recruitment processes. ED physicians will have the opportunity to enter a prize draw for a Starbucks® gift card by completing a paper ballot in the ED. After every fifth participant is recruited, a draw will be carried out for the ED physicians and a gift card will be awarded. Information about the study will be sent to ED nurses over email in an electronic newsletter.

Research personnel will maintain study records that are complete, legible and accurate so as to allow for appropriate interpretation, reporting and verification of study records.

Monitoring for this protocol will be coordinated by the sponsor - investigator. A Peer Monitor will monitor the study regularly. The plan will consist of monitoring for REB and regulatory compliance on-site and remotely through MICYRN, to ensure that the rights and well-being of participants are protected and reported data are accurate, complete and verifiable from source documents, along with the trial being conducted in compliance with the currently approved protocol and other applicable regulatory requirements. The peer monitoring activities will consist of, but not be limited to verification of:

- the investigator has adequate qualifications and resources,
- the investigational product(s) are stored, supplied, returned/disposed as per protocol and applicable regulatory requirement(s),
- the investigator follows the approved protocol and all protocol amendments,
- the written informed consent was obtained before each subject's participation, and was re-consented when amendments were made in the trial,
- the investigator receives current protocol amendments, all documents, and all trial supplies needed to conduct the trial properly,
- the investigator and the investigator's trial staff are adequately informed about the trial,
- the investigator and the investigator's trial staff are performing the specified trial functions in accordance with the protocol and written agreements,
- the investigator is enrolling only eligible subjects,
- the subject recruitment rate,
- the source documents and the other trial records are accurate, complete, and kept up-to-date and maintained,
- the investigator provides all of the required reports, notification, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial
- Checking the accuracy and completeness of the electronic CRF entries, source documents and other trial-related material,

- Informing the investigator of any electronic CRF entry error, omission, or illegibility in writing,
- Determining whether all adverse events are appropriately reported within the time periods required by GCP, the protocol, the REB, the sponsor, and applicable regulatory requirements,
- Determining whether the investigator is maintaining the essential documents,
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

## **13.2 Data Safety and Monitoring Board**

The data safety monitoring board (DSMB) will comprise three individuals: 1) a biostatistician from the CHEO research institute, 2) an epidemiologist from the CHEO research institute and, 3) an external emergency physician. The DSMB members will individually review the protocol prior to initiation of recruitment. Should any of the DSMB members have concerns about the protocol, a meeting will be called prior to initiating recruitment during which the DSMB members will make a decision about protocol approval. After the DSMB has approved the protocol and recruitment has begun, the DSMB will convene as necessary thereafter if and when safety issues arise.

Any safety concerns raised by clinical or research staff will be reported to the DSMB by the investigators in a written report as soon as possible. All serious adverse events will be brought to the attention of the DSMB immediately by the Qualified Investigator, who will also send a report to Health Canada (see section 11.4). Once safety issues have been brought to the attention of the DSMB, a meeting will be scheduled as soon as possible. Should the DSMB identify concerning trends in adverse events or should a serious adverse event requiring unblinding occur, they will contact the research pharmacists, at their discretion, to access participant information if required for safety reasons. The DSMB will make decisions regarding early trial termination. Should the DSMB make a decision for early trial termination or should the DSMB identify major concerns relating to safety in relation to the trial, the DSMB chair will prepare a written report and communicate the plans or findings both verbally and in written form to the study investigators.

## **13.3 Ethical Considerations**

### **13.3.1 General Principles**

This trial will be carried out according to the principles outlined in the Declaration of Helsinki(64), the ICH Good Clinical Practice Guidelines(51) and the Division 5 of Health Canada's Food and Drug Regulations. The institutional policies of the CHEO REB will also be followed.



Prior to initiating the study, written approval from the CHEO REB will be sought. Protocol deviations will only be implemented following approval from the CHEO REB, except where the investigators are concerned about potential hazards to the participants or where the deviations are logistical or administrative in nature.

### **13.3.2 Clinical Equipoise**

Although there is a large body of evidence to support the use of dexamethasone in adults for the prevention of migraine recurrence, there are no studies to date that have addressed the use of dexamethasone for this indication in children and adolescents. It is not uncommon that pediatric patients respond differently to medications than adults. Therefore, before clinicians adopt the use of medications with proven efficacy in the adult population, it is preferable to assess efficacy and safety in the pediatric population. For this reason, there is definite clinical equipoise regarding the use of dexamethasone for the prevention of migraine recurrence in the pediatric population. In addition, it is justifiable to use placebo as a comparison in this setting given that there are no known effective therapies for this indication.

### **13.3.3 Informed Consent**

Informed consent will be sought from all parents and participants aged 16 years and older. Additionally, informed assent will be sought from participants under the age of 16 years, or from those deemed by their physician and the research assistant to be cognitively unable to provide informed consent. All elements pertinent to consent and assent will be explained verbally to the parents and participants by the research assistant. Parents and participants will also be provided with a written informed consent form, and in applicable cases, with a written assent form. The consent and assent forms comply with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans(65) (see Appendices H, I and F). The consent discussions and forms use simple language, written and expressed at the grade 6 level. Language at the grade 3 level will be used for the assent process. Participants and their parents will receive a detailed explanation about potential harms incurred by the study, namely about potential side effects of dexamethasone and the inconvenience of the follow-up process with regards to time commitment. Anticipated benefits will also be discussed: 1) direct benefits: potential efficacy of dexamethasone in preventing migraine recurrence, the potential for a 10\$ gift card to Chapters Indigo should the participant complete all follow-up 2) indirect benefits: potential to be involved in research that might ameliorate the care of pediatric migraine patients in the ED.

### **13.3.4 Privacy and Confidentiality**

Participant information will be coded using study identification numbers. Participant data will be entered into the MICYRN study database using the study identification numbers, and will therefore be de-identified. Consent forms and contact information collected for the purposes of telephone follow-up will be stored separately from the rest of the data in a paper-based file that will be kept in a secure, locked area. Only the pharmacists carrying out randomization will have

access to the participants' group assignments in case there are adverse reactions that require unblinding. The names and their associated study identification numbers will be stored in a password-protected electronic file.

## **14. Budget and Finance**

This study will be funded through a Physicians' Services Incorporated Foundation grant.

## **15. Publication Plan**

A manuscript will be submitted for publication to a peer-reviewed medical journal and at least one conference abstract will be submitted for presentation. The listed investigators will participate in the drafting, review and dissemination of the manuscript and abstracts. Authors will be required to meet authorship criteria as laid out in the International Committee of Medical Journal Editors Guidelines (ICMJE).

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