WCHRI *Study:No OUCH*
Study Title *Version: 1.0*
Data Management Plan *Date:20 Mar 2019*

Study Details			
Study Title:	No-OUCH A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials		
Investigator:	Dr. Samina Ali	**Code:**	00073476
Sponsor:	University of Alberta		
Document History			
Version	**Date**	**Reason For Change**	
1	20 Mar 2019	Initial draft	

Introduction

This document defines the data management approach for the named study. Specifically it defines data sources, data handling practice and relevant additional documentation.

Document Control

This document is to be authorized by WCHRI DCC Team Lead, their designee or a senior manager within the Women & Children's Health Research Institute (WCHRI). The study sponsor (sponsor-initiated studies) and/or Principal Investigator (investigator-initiated studies) should also review and authorize the production version and any subsequent modifications.

Following authorization a read-only 'controlled' copy will be created and the document will be allocated a version number. Subsequent changes will be authorized (see above) and the version number incremented. Each authorized version will be retained on file for audit purposes.

Study Title

A Study of Non-Steroidal or Opioid Analgesia Use for Children with Musculoskeletal Injuries: The No OUCH Trials

Study Overview

This study will be comprised of two Phase 2, six-centre, randomized, double-blind, placebo-controlled trials that will be run simultaneously. The primary objective of this study is to determine the effectiveness of a combination of opioid and non-opioid oral analgesic medications (PO ibuprofen + PO acetaminophen; PO ibuprofen + PO hydromorphone; PO ibuprofen alone) for the acute pain management of children with an acute musculoskeletal (MSK) limb injury.

The study aims to recruit 536 children, aged 6-17 years, presenting to one of six Canadian pediatric emergency departments (EDs) with an acute MSK injury (<24 hours old) of a single limb over a period of 18 months.

Participants who participate in the Opioid Trail will receive either single-dose:

A. Oral hydromorphone (0.05mg/kg, max 5mg) + Oral ibuprofen (10mg/kg, max 600mg), OR
B. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR
C. Oral ibuprofen (10mg/kg, max 600mg)

Participants who participate in the Non-Opioid Trial will receive either single-dose:

A. Oral acetaminophen (15mg/kg, max 1000mg) + Oral ibuprofen (10mg/kg, max 600mg), OR

Ali, et al. BMJ Open 2020; 10:e035177. doi: 10.1136/bmjopen-2019-035177

B. Oral ibuprofen (10mg/kg, max 600mg)

Pain scores, any adverse events, level of sedation, and vital signs will be recorded every 30 minutes, for up to 120 minutes following study drug administration. Participants will also receive two follow-up questionnaires, either by email or telephone, at 24 hours and 1 week post discharge from the ED.

For inclusion and exclusion criteria see the study protocol.

Primary Efficacy Variables

Primary Efficacy Endpoint will be the self-reported pain score at 60 minutes, using a 0-10 verbal Numerical Rating Scale (vNRS).

Variable: pain_vnrs at the 60 minute mark

Secondary Efficacy Variables

The Secondary Efficacy Endpoints will include:

Endpoint	Variable Name
1. the proportion of patients with a vNRS pain score <3 at 60 minutes	pain_vnrs at the 60 minute mark
2. the proportion of patients with a vNRS pain score reduction of at least 2 points out of 10 at 60 minutes	pain_vnrs at the 60 minute mark
3. between group differences in pain scores at study time-points (T-30,T-60,T-90, T-120, T-Medical Exam and T-Xray)	pain_vnrs, pain_fpsr and pain_vas at all timepoints
4. self-reported caregiver and child satisfaction with pain relief and acceptability of study medications, using a previously employed 5 point Likert scale	qp_rate qp_relief qc_rate qc_same folup2_ratetx folup2_ratetx_expl folup2_relief folup2_relief_expl
5. ED length of stay	pscr_triage disch_dt
6. frequency of missed fractures or dislocations	disch_mddx disch_raddx
7. the proportion of children administered a rescue analgesic in the 60 minutes following administration of study medication	cm_sd cm_st cm_ed cm_et
8. time to effective analgesia, defined as the first vNRS pain score <3 post-intervention	pain_vnrs

9. children's self-reported pain intensity on the Visual Analog Scale (VAS) and the Faces Pain Scale-Revised (FPS-R) at all study times	pain_vas pain_fpsr

Safety Data

Principal Safety Endpoint will be the proportion of children with any adverse events related to study drug administration.

Secondary Safety Endpoints will include 1. the proportion of children with any serious adverse events during the study period, 2. the proportion of children in each study group with a Ramsay Sedation Score (RSS) score between 1 to 3, and 3. the proportion of children with each specific adverse event type during the study period.

Patient Numbers

The sample size for the three-armed Opioid Trial is 105 patients per arm, for a total of 315. For the two-armed Non-Opioid Trial, a sample of 85 patients per arm, for a total of 170. Thus, the grand total for the No OUCH Study would be 485. In order to account for patients who are excluded from primary analyses due to missing data for the primary (efficacy) outcome and to adjust for loss to follow-up, the sites will recruit approximately 10% more, for a target recruitment of approximately 536 patients. However, in order to preserve the patient preference aspect of this study, which allows families to choose which trial they would like to participate in, we will over-recruit one trial in order to allow the second to achieve its sample size.

Study Timelines

Participants are enrolled, if eligible, in the ED. Once the drug is administered, patient assessments are implemented in the ED at T0, T30, T60, T90 and T120 time points. Assessments are also collected at the time of the medical examination, time of x-rays and at discharge. Two follow-ups conducted either by phone or online survey to be completed at 1-3 days post discharge and 1-2 weeks post discharge. Total study period: 14 days for all outcome data.

First Participant visit: April 2019

Last Participant visit: expected April 2021

Ethics Status

This is a Health Canada regulated clinical trial that requires REB approval at participating sites. It is required to be GCP-compliant and undertaken on a validated installation of REDCap.

Data Sources

All data entry will be performed at the sites by trained research staff, with exception of the survey data which will be entered directly by the parents. Source Documents include medical records. Some data will be collected directly from the study participants and under these circumstances REDCap is considered the source document.

Standard Operating Procedures

Data management work performed by WCHRI will be undertaken using the current version of WCHRI SOPs.

Scope of Work

WCHRI staff will perform the following tasks:

Database build, data management activities, delivery of data for analysis, preparation of DSMB reports.

Data Collection Mode

Data will be collected electronically (any transcription from paper will be performed at the study sites. WCHRI will not receive copies of paper CRFs or source documents.)

CRF Design

Data collection forms have been developed by the Principal Investigator and her staff with minimal input from WCHRI.

Data Collection System

Data will be entered into REDCap by personnel at the study sites.

Randomization and Unblinding

For Randomization and Unblinding specifics, see the protocol.

Randomization of participants will occur outside of REDCap. Should unblinding be required, this will be performed through the study unblinding project in REDCap. In addition, 1-3 days AFTER The primary outcome measures are collected, the study arm assigned to the patient will be revealed.

Study Monitoring

Monitoring will be performed by staff from the University of Alberta Quality Management in Clinical Research (QMCR) according to their monitoring plan.

Document Tracking

WCHRI will not be handling paper documents for this study.

Data Entry

The Study sites will complete electronic CRFs contained within the data collection system (REDCap) based on the contents of the patient records and other data sources.

Data Handling

Data handling practices for this study are documented in the study's data handling manual. This document will be updated throughout the study as practices are refined and as new situations arise. Specifically, this document covers issues such as data handling conventions, self-evident corrections, data query practice and will also serve to log data handling exceptions.

Data Quality

Ali S, *et al. BMJ Open* 2020; 10:e035177. doi: 10.1136/bmjopen-2019-035177

The approach to data quality is based on key points contained within ICH GCP. These are:

- Complete Minimal missing values
- Accurate Database values match original observation
- Precise Units and measurability clearly understood
- Timely Minimal time between observation and recording

- Verifiable Independent assessment or monitoring
- Traceable Actions taken are logged

The above points will be ensured as follows:

Data Validation and Queries

Electronic data collection forms will be programmed with online validation checks (also known as edit checks). Based on an understanding of the data collection forms these checks will:

- Alert data entry users to missing data
- Check that numeric variables and dates are within reasonable ranges
- Check for consistency within the data

Entered data will be subject to visual and electronic validation by data management staff according to an approved data validation plan. Issues that arise will be notified to the sites as queries, for resolution.

Data issues will be entered into the data capture system in the form of queries/discrepancies. Sites will respond to the queries, directly in the data collection system. Query responses will be reviewed by data management staff and closed once the issue has been resolved.

Source Document Verification

This will be performed by study monitors according the approved monitoring plan.

Serious Adverse Events

Serious adverse events (SAEs) are to be reported to the sponsor *(and/or PI for investigator-initiated studies)* and ethics board, by the sites, as defined in the study protocol. Periodically the sponsor (or PI) will forward copies of SAE reports to WCHRI for reconciliation with the CRF data.

Data Coding

Adverse events will be coded with MedDRA by WCHRI staff. A formal coding review will be undertaken by an authorized individual prior to database lock or delivery for interim analysis.

Data Extract and Delivery

Data will be extracted into SAS data sets for delivery to the study statistician.

Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The DMSB will operate under the rules of an approved charter which will outline all terms of reference, as well as the frequency of meetings, that will be reviewed at the organizational meeting of the DSMB. Prior to each DSMB meeting, the study statistician shall prepare reports with interim data for presentation to the DSMB.

Ali S, *et al. BMJ Open* 2020; 10:e035177. doi: 10.1136/bmjopen-2019-035177

The following timelines will need to be met in order to have enough time to prepare and submit the report to the DSMB.

- Data quality review will be performed 6-8 weeks prior to the data of the planned DSMB meeting and any necessary queries raised.
- Study sites will be asked to review and respond to queries within 1-2 weeks

- 4-5 weeks before the DSMB meeting data will be exported and provided to the statistician for preparation of the DSMB reports.

Archiving and Destruction

After study completion all study materials will be returned to the Principal Investigator / Sponsor for archiving.

Electronic data will be retained in WCHRI secure systems until such time as these systems are decommissioned or until the Principal Investigator requests their deletion.

Tasks and Responsibilities

These are summarized in the following table:

Task	Responsibility	Notes
CRF design	PI	
Database configuration	WCHRI	
Database documentation	WCHRI	
Database acceptance testing	WCHRI / PI	
Monitoring	CRU	
Document flow and tracking	N/A	
Data entry	Study sites	
Data validation	WCHRI	
Discrepancy resolution	Study sites	
Data extract	WCHRI	
Analysis database creation	WCHRI	
DSMB Reports	WCHRI	
Study materials archiving	Study sites / PI	
Data archiving	PI	

Authorization:

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Authorized by: (PI or Sponsor) Dr. Samina Ali **Date:** 15 April 2019