

AWARD NUMBER: W81XWH-17-1-0665

TITLE: Prevention of Post-Traumatic Contractures with Ketotifen II (PERK 2)

PRINCIPAL INVESTIGATOR: Kevin A. Hildebrand

CONTRACTING ORGANIZATION: Governors of the University of Calgary
2500 University Drive NW
Calgary, Alberta CANADA
T2N 1N4

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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1. REPORT DATE Oct 2020		2. REPORT TYPE Annual		3. DATES COVERED 30/09/2019 - 29/09/2020	
4. TITLE AND SUBTITLE Prevention of Posttraumatic Contractures with Ketotifen II (PERK2)				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-17-1-0665	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Kevin A. Hildebrand E-Mail: hildebrk@ucalgary.ca				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Governors of the University of Calgary 2500 University Drive NW Calgary, Alberta CANADA T2N 1N4				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Regulatory approvals - US Food and Drug Administration, USAMRMC Human Research Protections Office (HRPO), Health Canada - have been completed for 14 participating sites. Remaining 3 sites are poised for approval during Q1 of year 4. 14 of the participating sites have received ethics approval. Site initiation visits were completed at 6 sites, with 11 actively recruiting before COVID-19 lockdown. Bay Area Research Logistics (BARL) has completed shipment of medication to 11 sites, with plans on shipping medication to 3 more sites during Q1 of year 4. These efforts have led to active sites successfully recruiting and randomizing 51 participants. Screening/recruitment efforts have been limited due to COVID-19 restrictions at all sites of interest. Only 6 sites have been approved for trial restart by the local operating officials. However, all sites with active participants were able to safely continue data collection efforts. Site contract negotiations have been completed at 16 sites, with the last remaining to be done during Q1 of Year 4. Bi-weekly safety summary meetings are being held with local Research Monitor to review AE/SAE's. Updated versions of charters for Data Monitoring Committee (DMC), Trial Steering Committee (TSC), and Trial Management Group (TMG) were finalized. Monthly TMG meetings are being held, with TSC meetings occurring every three months. DMC membership has been finalized, with plans of holding first meeting during Q1 of Year 4. One manuscript was published during this reporting period.					
15. SUBJECT TERMS Randomized Clinical Trial; Multicenter; Placebo; Ketotifen; Contractures; Post-traumatic; Elbow fractures or dislocations; Surgery; Range of motion; Disability Arm Shoulder Hand; Oxford Elbow Score; Pain Catastrophizing Scale.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 128	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

This proposal pertains to the FY16 PRORP CTA Focus Area on Surgical Care – Extremity Fractures. This research optimizes patient outcomes through prevention of post-traumatic joint contractures following fractures. We are conducting a multicenter, multidose randomized clinical trial comparing Ketotifen fumarate to a Lactose placebo started within 7 days of elbow fractures or dislocations. The primary outcome measure is elbow extension-flexion arc range of motion 12 weeks after randomization. Secondary outcome measures are range of motion at other selected time points and patient reported outcome measures at these time points and 12 weeks.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Randomized Clinical Trial; Multicenter; Placebo; Ketotifen; Contractures; Post-traumatic; Elbow fractures or dislocations; Surgery; Range of motion; Disability Arm Shoulder Hand; Oxford Elbow Score; Pain Catastrophizing Scale

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Major Task 1: Complete Clinical Trial Development Award – this was OR140142

Major Task 2: Phase III RCT Implementation

Major Task 3: Study Performance

Major Task 4: Knowledge Translation

What was accomplished under these goals?

Major Task 1: Complete CTDA OR140142

1. Major Activities:

- a. Regulatory Compliance
- b. Core Study Functions
- c. Recruiting Sites

2. Specific Objectives:

- a. Complete contract negotiations with recruiting sites.
- b. Obtain Ethics Internal Review Board and Department of Defense Human Research Protection Office (HRPO) approval for 17 participating sites.

3. Results:

- a. Contracts completed and signed off for the following sites. **See appendices pages 15 – 24:**
 - i. Carolina’s Medical Center
 - ii. Saint Joseph’s Hospital
 - iii. Sunnybrook Health and Sciences Centre
 - iv. University of Vermont Medical Center
- b. Ethic board approvals were received for the following sites. **See appendices pages 25 – 29:**
 - i. Sunnybrook Health and Sciences Centre
 - ii. Queen Elizabeth II Health and Sciences Centre
- c. Human Research Protection Office (HRPO) submission approvals were received for the following sites. **See appendices pages 30 – 41:**
 - i. Queen Elizabeth II Health and Sciences Centre
 - ii. Sunnybrook Health and Sciences Centre
 - iii. Saint Joseph’s Hospital
 - iv. Saint Paul’s Hospital
- d. Initial Investigational Product shipments completed through BARL to the following sites. **See appendices pages 42 – 46:**
 - i. The Ottawa Hospital – Civic Campus
 - ii. The Ottawa Hospital – General Campus
 - iii. University of Vermont Medical Center
 - iv. Saint Paul’s Hospital
 - v. Saint Joseph’s Hospital

Major Task 2: Phase III RCT Implementation

1. Major Activities:
 - a. Organizational Transitions
 - b. Site Initiations
 - c. Organizing Screening, Enrollment and Randomization Procedures
2. Specific Objectives:
 - a. Start at Calgary Sites
 - b. Site roll out outside of Calgary
3. Results:
 - a. Site initiation visits completed at the following sites. **See appendices pages 47 – 63:**
 - i. The Ottawa Hospital – Civic Campus
 - ii. The Ottawa Hospital – General Campus
 - iii. University of Vermont Medical Center
 - iv. Saint Paul’s Hospital
 - v. Saint Joseph’s Hospital
 - vi. Carolina’s Medical Center
 - vii. Sunnybrook Health and Sciences Centre
 - b. Following site initiations visits, official enrolment and randomization procedures started at 11 sites. As a result, 51 participants have been recruited and randomized into the clinical trial. Appendix reflects 51 participants randomized by the end of the reporting period. **See appendices page 64 – 65.**

Major Task 3: Study Performance

1. Major Activities:
 - a. Trial Committees
 - b. Support Organizations
2. Specific Objectives:
 - a. Three performance committees meetings
 - b. Regular meetings with Core facilities – EPICORE, CIPAC, BARL
3. Results:
 - a. Charters for Data Monitoring Committee (**See pages 66 – 78**), Trial Management Committee (**See pages 79 – 87**), and Trial Steering Group (**See pages 88 – 96**) were finalized.
 - b. Monthly Trial Management Group (TMG) meetings were held during this reporting period. **See appendices pages 97 - 103.**
 - c. Trial Steering Committee (TSC) meetings were held during this reporting period. **See appendices pages 104 – 109.**
 - d. Prospective Data Monitoring Committee members approached and confirmed. **See appendices pages 110 – 117.**

Major Task 4: Knowledge Translation

1. Major Activities:
 - a. Publications/Meetings
 - b. Trial Results
 - c. Site Engagement and Updates
2. Specific Objectives
 - a. Trial protocol manuscript, Specialty meetings abstracts and attendance
 - b. Trial results – Primary paper, secondary papers, presentations specialty societies
 - c. Site engagement
3. Results
 - a. One manuscripts coauthored by the graduate student Ayo Ademola published by BMC Musculoskeletal Disorders. **See appendices pages 118 – 125.**
 - b. Monthly PERK 2 newsletter continued through the year. **See appendices pages 126 – 128.**

What opportunities for training and professional development has the project provided?

Graduate Student Ayo Ademola, PhD candidate, Department of Community Health Science, University of Calgary. Training received included writing and publishing the PERK 2 protocol manuscript by BMC Musculoskeletal Disorders. See appendices pages 118 – 125.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

The main objectives for the year are to complete post COVID-19 lockdown restart procedures and continue steady recruitment at 11 active sites, with subsequent start of three more sites at the beginning of Year 4, Quarter 1. In regards to regulatory compliance leading to site start-ups, our objective is to complete all procedures involved for the 3 remaining sites by Year 4, Quarter 2. Continuing the TMG and TSC meeting, and running the first DMC meeting during Year 4, Quarter 1. Regular meetings with the support organizations CIPAC, BARL, and EPICORE. Finally, continuing manuscript and presentation development, with eyes set in further literature development efforts towards Year 4, Quarter 2.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

- 5. CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Further efforts are in development to address current and future effects of the COVID-19 pandemic on trial procedures. By the end of this reporting period, modifications were completed to address COVID-19 risks and measures outlined by local REB authorities. Eyes are set on adding a protocol modification including a guidance document that better adapts trial procedures to current and future needs in light of COVID-19.

Actual or anticipated problems or delays and actions or plans to resolve them

After achieving great strides in completing start-up procedures for 11 of 17 sites, recruitment rate was gaining a steady pace. Our hopes were to finalize regulatory needs for all 17 sites by the end of Year 3, Quarter 2, when the COVID-19 pandemic/lockdown was put into place. To address the safety of trial staff and participants, Sponsor decided to stop screening and recruitment from March 18th, 2020 until July 1st, 2020, when some sites were able to begin trial restart tasks. Even though sites were able to continue remote data collection procedures through lockdown, the first restart procedures at certain sites were only possible after almost five months from the beginning of the COVID-19 lockdown. We continue to work hard on getting all sites back to normal, with six sites restarting screening/recruitment activities by the end of this reporting period. Restart has resulted in 5 new recruits within a month. However, ongoing restrictions will lead to further delays in achieving recruitment rates previously predicted.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Publication of the PERK 2 manuscript paper by BMC Musculoskeletal Disorders. **See appendices pages 118 – 125.**

Ademola, A., Hildebrand, K., Schneider, P., Mohtadi, N., White, N., Bosse, M., Garven, A., Walker, R., & Sajobi, T. (2020). PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2) – protocol for a multicenter randomized clinical trial. BMC Musculoskeletal Disorders. 21. 10.1186/s12891-020-3139-2.

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Kevin Hildebrand
Project Role:	Principal Investigator
Research Identifier:	
Nearest Person Month worked:	12
Contribution to Project:	Overall management. Writing grants, study design. Recruiting sites. Obtaining data management, medication partners.
Funding Support:	Department of Surgery University of Calgary
Name:	Gerardo Duque
Project Role:	Research Coordinator
Research Identifier:	None
Nearest Person Month worked:	12
Contribution to Project:	Regulatory application (IND, HRPO, Health Canada). Database Development and quality assurance. Case report forms consent writing. Screening, recruitment, randomization, and participant follow ups. Contracts. Institutional Review Board processing.
Funding Support:	Department of Defense.
Name:	Taylor Stranaghan
Project Role:	Clinical Research Assistant
Research Identifier:	None
Nearest Person Month Worked:	4.5
Contribution to Project:	Clinical trial implementation and ongoing development. Screening, recruitment, randomization, and participant follow ups. Case report form development. Institutional Review Board processing.
Funding Support:	Department of Defense

Name:	Nicole Foldessy
Project Role:	Clinical Research Assistant
Research Identifier:	None
Nearest Person Month worked:	1.5
Contribution to Project:	Clinical trial implementation and ongoing development. Screening, recruitment, randomization, and participant follow ups. Case report form development. Institutional Review Board processing.
Funding Support:	Department of Defense

Name:	Tolulope Sajobi
Project Role:	Trial Statistician
Research Identifier:	
Nearest Person Month worked:	1
Contribution to Project:	Statistical support. Recruitment and co-supervise PhD student.
Funding Support:	Department of Community Health Sciences, University of Calgary

Name:	Ayoola Ademola
Project Role:	PhD Graduate Student
Research Identifier:	None
Nearest Person Month worked:	1
Contribution to Project:	Statistical support
Funding Support:	Department of Defense

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

Organization Name:	Bay Area Research Logistics
Location:	Hamilton, ON, CANADA
Contribution:	Sourcing Ketotifen, Lactose Placebo, manufacturing and distribution study medication
Organization Name:	EPICORE Centre
Location:	University of Alberta, Edmonton, AB, CANADA
Contribution:	Development of RedCap Electronic Data Capture, Randomization process (Drug Tracking System), Project management, servers to support study
Organization Name:	Calgary Image Processing and Analysis Centre
Location:	Calgary, AB, CANADA
Contribution:	Archiving and analysis centre for radiographic evaluation of fracture healing
Organization Name:	Alberta Health Services
Location:	Peter Lougheed Centre, Calgary, AB, CANADA
Contribution:	Office space, computer support, clinic space for recruitment and follow up of participants

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments. See **appendices page 14**.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Prevention of Post-Traumatic Contractures with Ketotifen II (PERK II)

OR160026

W81XWH-17-1-0665



PI: Kevin A. Hildebrand

Org: Governors of the University of Calgary

Award Amount: \$2,440,796

Study/Product Aim(s)

- Major Task I: Complete Clinical Trial Development Award – CTDA (OR140142)
- Major Task 2: Phase III RCT Implementation
- Major Task 3: Study Performance
- Major task 4: Knowledge Translation

Approach

PERK II is a multicenter RCT led from Calgary, CANADA with US centers included. Completing the CTDA will have the infrastructure in place to perform the RCT. This trial will compare 2 different doses of ketotifen fumarate to a lactose placebo in preventing post-traumatic contractures following elbow injuries that require an operation. The medication is randomized, while operation requirement is not.



51 participants recruited by the first week of October. There are currently six sites able to screen/recruit participants. Other sites are in process of restarting activities post-COVID-19 restrictions. Three more sites currently finalizing regulatory procedures to be able to screen/recruit during Q1 of Year 4. Last site contract negotiation to be completed during Q1 of Year 4.

Timeline and Cost

Activities	CY	17	18	19	20
Complete CTDA					
Phase III RCT Implementation					
Study Performance					
Knowledge translation					
Estimated Budget (\$K)		\$154	\$638	\$704	\$536

Updated: (September 29th, 2020)

Goals/Milestones

CY17 Goal – Complete CTDA

- ☒ IND Approval
- ✓ Database and Medication Manufacture Development

CY18 Goals – Regulatory/IRB/Contracts

- ✓ PLC completed all steps
- ✓ Other sites in progress

CY19 Goal – Continue recruitment

- ☐ Complete CTDA
- ✓ Recruit first participant
- ✓ Add other sites

CY20 Goal – Continue recruitment, follow up

- ☐ All sites recruiting

Comments/Challenges/Issues/Concerns

Post COVID-19 site restarts in progress since August, 2020. 6/17 sites currently screening/recruiting.

Budget Expenditure to Date

Projected Expenditure: \$2,032,775

Actual Expenditure: \$680,564

SUB-SITE AGREEMENT

This Agreement is made and entered into as of the last date of signature by all parties ("Effective Date").

AMONGST:

Dr. Kevin Hildebrand of Calgary, Alberta

(the "PRINCIPAL INVESTIGATOR")

OF THE FIRST PART,

- and -

The Governors of the University of Calgary

2500 University Drive NW, Calgary, Alberta, Canada, T2N 1N4

(the "PRINCIPAL INSTITUTION")

OF THE SECOND PART,

-and-

The Charlotte-Mecklenburg Hospital Authority d/b/a Atrium Health

1000 Blythe Blvd., Charlotte, NC 28203-5812

(the "SUB INSTITUTION")

OF THE THIRD PART

(The PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION, and SUB INSTITUTION may collectively be referred to as "Parties" and individually as a "Party".)

WHEREAS the PRINCIPAL INVESTIGATOR has received a grant from Department of Defense office of the Congressionally Directed Medical Research Programs ("Funding Source") in support of performing a clinical study entitled: "PrEvention of post-traumatic contractuRes with Ketotifen 2 (PERK 2)" ("Clinical Study").

WHEREAS the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR have entered into an agreement with the Funding Source ("Prime Agreement") attached as ATTACHMENT "A".

WHEREAS the SUB INSTITUTION, on behalf of its employee, Dr. Michael Bosse ("SUB-INVESTIGATOR") has agreed to participate in the Clinical Study.

AND WHEREAS the Parties hereto wish to reduce to writing their agreement with respect to the conduct of the Clinical Study at the SUB INSTITUTION (the "Agreement").

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

PRINCIPAL INVESTIGATOR:

Signature: _____

Dr. Kevin Hildebrand

March 4, 2020

_____ Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____

Marcello Tonelli

Senior Associate Dean, Health Research

MAR 03 2020

_____ Date

SUB INSTITUTION:

Authorized

DocuSigned by:

Michael R. Gibbs

Signatures: _____

DFD6776AED4B4DE...

Michael Gibbs, MD, Interim VP, Research

2/27/2020

_____ Date

SUB INVESTIGATOR READ AND ACKNOWLEDGED:

Signature: _____

Dr. Michael Bosse

DocuSigned by:

Michael Bosse

633F6D41C4054C9...

2/25/2020

_____ Date

SUB-SITE AGREEMENT

This Agreement is made and entered into as of the last date of signature by all parties ("Effective Date").

AMONGST:

Dr. Kevin Hildebrand of Calgary, Alberta
(the "PRINCIPAL INVESTIGATOR")

OF THE FIRST PART,

- and -

The Governors of the University of Calgary
2500 University Drive NW, Calgary, Alberta, Canada, T2N 1N4
(the "PRINCIPAL INSTITUTION")

OF THE SECOND PART,

-and-

Dr. Graham King
St. Josephs Health Care London
268 Grosvenor St. PO Box 5777, Stn B, D0-202
London, OnN6A 4V2
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

**Lawson Health Research Institute, a joint venture of London Health Sciences Centre Research Inc.
and Lawson Research Institute**
750 Base Line Road East, Suite 300, London, Ontario, Canada, N6C 2R5
(the "SUB INSTITUTION")

OF THE FOURTH PART

(The PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION, SUB INVESTIGATOR and SUB INSTITUTION may collectively be referred to as "Parties" and individually as a "Party".)

WHEREAS the PRINCIPAL INVESTIGATOR has received a grant from Department of Defense office of the Congressionally Directed Medical Research Programs ("Funding Source") in support of performing a clinical study entitled: "PrEvention of post-traumatic contractuRes with Ketotifen 2 (PERK 2)" ("Clinical Study"). The PRINCIPAL INVESTIGATOR is the regulatory sponsor of the Clinical Study.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

PRINCIPAL INVESTIGATOR:

Signature: 
Dr. Kevin Hildebrand

November 13 2019.
Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: 
Marcello Tonelli
Senior Associate Dean, Health Research

NOV 14 2019

Date

SUB INVESTIGATOR:

Signature: _____
Dr. Graham King

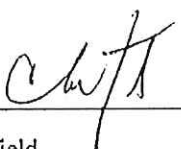
Date

SUB INSTITUTION:

LAWSON HEALTH RESEARCH INSTITUTE

London Health Sciences Centre Research Inc.

Authorized

Signatures: 
Cheryl Litchfield
Manager, Grants & Contracts

Oct 24, 19
Date

Reviewed by D.C.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

PRINCIPAL INVESTIGATOR:

Signature: _____

Dr. Kevin Hildebrand

Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____

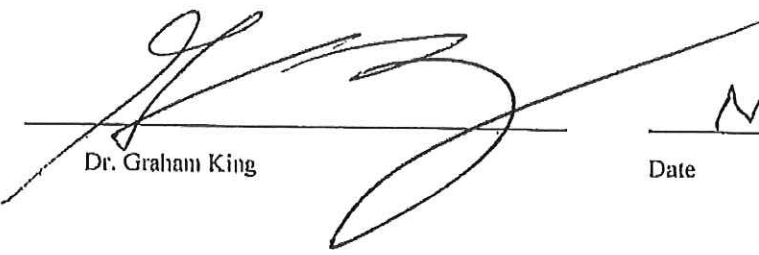
Marcello Tonelli

Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____


Dr. Graham King

Nov 7/19

Date

SUB INSTITUTION:

LAWSON HEALTH RESEARCH INSTITUTE

London Health Sciences Centre Research Inc.

Authorized

Signatures: _____


Cheryl Litchfield

Manager, Grants & Contracts

Oct 24/19

Date

Reviewed by D.C.

Lawson Research Institute

Authorized

Signature:


Cheryl Litchfield
Manager, Grant & Contracts

Date 

SUB-SITE AGREEMENT

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AMONGST:

Dr. Kevin Hildebrand of Calgary, Alberta
(the “PRINCIPAL INVESTIGATOR”)

OF THE FIRST PART,

- and -

The Governors of the University of Calgary
2500 University Drive NW, Calgary, Alberta, Canada, T2N 1N4
(the “PRINCIPAL INSTITUTION”)

OF THE SECOND PART,

-and-

Dr. Diane Nam
Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Room MG 361, Toronto, Ontario, M4N 3M5
(the “SUB INVESTIGATOR”)

OF THE THIRD PART,

-and-

Sunnybrook Research Institute
2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5
(the “SUB INSTITUTION”)

OF THE FOURTH PART

(The PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION, SUB INVESTIGATOR and SUB INSTITUTION may collectively be referred to as “Parties” and individually as a “Party”).

WHEREAS the PRINCIPAL INVESTIGATOR has received a grant from Department of Defense office of the Congressionally Directed Medical Research Programs (“Funding Source”) in support of performing a clinical study entitled: “PrEvention of post-traumatic contractuRes with Ketotifen 2 (PERK 2)” (“Clinical Study”, or “Study”).

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

PRINCIPAL INVESTIGATOR:

Signature: 
Dr. Kevin Hildebrand

August 5, 2020
Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: 
Marcello Tonelli
Senior Associate Dean, Health Research

July 28, 2020
Date

SUB INVESTIGATOR:

Signature: 
Diane Nam, MD

Jul 17, 2020
Date

SUB INSTITUTION:

SUNNYBROOK RESEARCH INSTITUTE

Signature: *Kullervo Hynynen*
Kullervo Hynynen (Jul 27, 2020 12:38 EDT)
Name: Kullervo Hynynen, Ph.D.
Title: Vice President Research & Innovation

Jul 27, 2020
Date

Signature: *Rod Engeland*
Rod Engeland (Jul 27, 2020 09:44 EDT)
Name: Rod Engeland
Title: Executive Director, Research Operations & Finance

Jul 27, 2020
Date

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(the "PRINCIPAL INVESTIGATOR")

OF THE FIRST PART,

- and -

The Governors of the University of Calgary

2500 University Drive NW, Calgary, Alberta, Canada, T2N 1N4

(the "PRINCIPAL INSTITUTION")

OF THE SECOND PART,

-and-

University of Vermont and State Agricultural College

(the "SUB INSTITUTION")

OF THE THIRD PART

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IN WITNESS WHEREOF, the Parties hereto have executed this Agreement as of the Effective Date.

PRINCIPAL INVESTIGATOR:

Signature: _____



Dr. Kevin Hildebrand

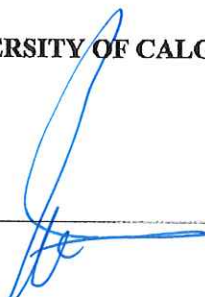
Oct 30, 2019

Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____



Marcello Tonelli

Senior Associate Dean, Health Research

NOV 04 2019

Date

SUB INSTITUTION:

University of Vermont and State Agricultural College

Authorized

Signatures: _____

Emily Trantum

Emily Trantum

Team Lead, Award Acceptance

Sponsored Project Administration

10/30/2019

Date

To: Dr. Diane Nam
Orthopaedic Surgery
Room MG361

From: Dr. Brian J. Murray

Date: October 25, 2019

Subject: **Prevention of Posttraumatic Contractures with Ketotifen 2 (PERK 2)**

Project Identification Number: 313-2019

Approval Date: October 25, 2019

Expiry Date: October 25, 2020

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted a Full Board review of the research study referenced above and approved the involvement of human participants. REB members involved in the research project or who have declared a conflict do not participate in the review, discussion or decision. All other required institutional approvals must also be obtained prior to the conduct of the study at this research site.

The approval of this study includes the following documents:

- PERK 2 Protocol Version 4.0 dated July 31, 2018
- Informed Consent form Version dated October 15, 2019
- Participant Medication & Study Drug Diary Version dated October 18, 2019
- Participant Wallet Card Version 1.0 dated July 18, 2018
- Drug Information Sheet Version 1.0 dated 2018/12/05
- CRF Version 1.5 dated August 2018
- DASH dated 2006 (English, French, Spanish (Chile, Dominican Republic, Puerto Rico, Spain)
- OES dated 2008 (English, French, Spanish USA)
- PCS dated 1995 (English, French)
- PCS Spanish USA dated May 5, 2017
- PCS-CF French, dated 1995



Nova Scotia Health Authority Research Ethics Board

Centre for Clinical Research, Room 118

5790 University Avenue

Halifax, Nova Scotia, Canada B3H 1V7

shelleyl.macdonald@nshealth.ca

November 27, 2019

Dr. Andrew Trenholm
Medicine\Surgery\Orthopedic Surgery
Room 4510, HI 1796 Summer Street Halifax, NS B3H

**Full Board Review
Full Approval Letter
(September 30, 2019- September 30, 2020)**

Dear Dr. Trenholm

RE: PrEvention of posttraumatic joint contractuRes with Ketotifen 2 (PERK 2)

NSHA REB ROMEO File #: 1025044

Thank you for your response regarding your proposed study.

Document Name	Comments	Version Date
Consent Form	consent v1 (clean)	2019/11/07
Consent Form	consent v1 (highlighted)	2019/11/07
Consent Form	pregnant partner consent	2019/11/07
Supporting Materials	updated drug info sheet (clean)	2019/11/07
Supporting Materials	updated drug info sheet (highlighted)	2019/11/07
Health Canada Letter of Authorization / No Objection Letter (NOL)	Correspondence with HC RE: v4 NOL for protocol	
Investigator Response/Revisions	reply to ethics	2019/11/07

I have reviewed these documents on behalf of the Research Ethics Board (REB) and note that all requested changes have been incorporated.

I am now pleased to confirm the Board's full approval for this research study, effective today. This includes approval / favorable opinion for the following study documents:

Document Name	Comments	Version Date
Researcher's Checklist for Submission	checklist	2019/09/10

Letter of Support	LOS - PI Dept	2019/09/12
Health Canada Letter of Authorization / No Objection Letter (NOL)	Health Canada NOL	2019/08/09
Radiological Review Application	Rad Rev approval	2009/12/19
Radiological Review Application	Rad Rev - approved consent risk wording	
Review Comments/Correspondence	lead site amended documents approval MOD4	2018/09/11
Review Comments/Correspondence	lead site amended documents approval MOD3	2017/09/11
Review Comments/Correspondence	Lead site amended documents approval MOD1	2018/11/09
Review Comments/Correspondence	lead site amended documents approval MOD2	2017/09/11
Review Comments/Correspondence	Lead Site (Calgary) ethics approval	2017/11/07
Consent Form	consent v1 (clean)	2019/11/07
Consent Form	consent v1 (highlighted)	2019/11/07
Consent Form	pregnant partner consent	2019/11/07
Research Protocol	protocol v4.0	2019/08/14
Supporting Materials	DASH questionnaire	
Supporting Materials	OES questionnaire	
Supporting Materials	phone call script	2019/02/08
Supporting Materials	V1 - wallet card	2018/07/18
Supporting Materials	PCS questionnaire	
Supporting Materials	home exercise program	
Supporting Materials	Medication diary page 1	
Supporting Materials	Medication diary page 2	
Supporting Materials	updated drug info sheet (clean)	2019/11/07
Supporting Materials	updated drug info sheet (highlighted)	2019/11/07
Health Canada Letter of Authorization / No Objection Letter (NOL)	Correspondence with HC RE: NOL for protocol v4	
Product Information	product monograph - ketotifen	2012/08/15
Current License to Practice in NS	PI license	2019/12/31
Certificate of Completion TCPS 2: CORE	PI TCPS2	2012/09/23
Curriculum Vitae (CV)	PI abbrev. CV	2019/09/13
SOP	Consent SOP	2013/06/12
Investigator Response/Revisions	reply to ethics	2019/11/07

Continuing Review

1. The Board's approval for this study will expire one year after the date of full Board review (September 30, 2020). To ensure continuing approval, submit a Request for Annual Approval to the Board 2-4 weeks prior to this date. If approval is not renewed prior to the anniversary date, the Board will close your file and you must cease all study activities immediately. To reactivate a study, you must submit a new Initial Submission (together with the usual fee) to the REB and await notice of re-approval.

2. Please be sure to notify the Board of any:

- Proposed changes to the initial submission (i.e., new or amended study documents or supporting

materials),

- Additional information to be provided to study participants,
- Material designed for advertisement or publication with a view to attracting participants,
- Serious unexpected adverse reactions experienced by local participants,
- Unanticipated problems involving risks to participants or others,
- Sponsor-provided safety information (e.g., reports of serious unexpected adverse reactions, changes to the investigator's brochure / product monograph, DSMB reports)
- Additional compensation available to participants,
- Upcoming audits / inspections by a sponsor or regulatory authority,
- Premature termination / closure of the study (within 90 days of the event).

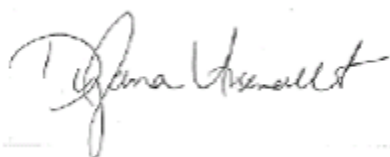
3. Approved studies may be subject to internal audit. Should your research be selected for audit, the Board will advise you and indicate any other requests at that time.

Important Instructions and Reminders

1. Submit all correspondence to Ethics Coordinator, Shelley MacDonald at the address listed at the top of this letter (do not send your response to the REB Chair or Co-Chair).
2. Login to the Research Portal; click Applications (Post Review), browse through files to locate the study in which you wish to make revisions to; click the Events Button and choose the type of revision you wish to make from the table provided; complete the electronic form and attach document under the attachments tab if required and Click on the Submit button.
3. Be sure to reference the Boards assigned file number, Romeo No. 1025044, on all communications.
4. Highlight all changes on revised documents, and remember to update version numbers and/or dates.

Best wishes for a successful study.

Sincerely,



Dylana Arsenault, BScBio, BScPharm, ACPR, PharmD
Co-Chair, NSHA Research Ethics Board

This statement is in lieu of Health Canada's Research Ethics Board Attestation:

The Research Ethics Board for the Nova Scotia Health Authority operates in accordance with:

- Food and Drug Regulations, Division 5 "Drugs for Clinical Trials Involving Human Subjects"
- Natural Health Products Regulations, Part 4 "Clinical Trials Involving Human Subjects"
- ICH Good Clinical Practice: Consolidated Guideline (ICH-E6)
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)

cc: Research & Innovation

The Board acknowledges receipt of the following documents:

- Health Canada NOL dated August 9, 2018
- Product Monograph ketotifen fumarate dated August 15, 2012
- FDA letter regarding removal of full clinical hold as of November 13, 2017
- PERK Pilot – Abstract from ASSH dated September 9, 2017
- Pre-Clinical Research Paper from JBJS dated June 2010

As Principal Investigator you are responsible for the ethical conduct of this study which may be subject to review by Quality Assurance and Education. The study must comply with current legislation outlined in the Ontario Personal Health Information Protection Act (PHIPA) and all acts, regulations, guidelines and policies that govern this research. Note that regional or provincial ‘shared systems’ that may be accessible from Sunnybrook systems (e.g. cGTA/Connecting Ontario from SunnyCare) cannot be used for research purposes (unless approved by the institution in limited circumstances).

The REB requires immediate notification of internal serious adverse events and significant deviations, submission of a renewal form prior to the approval expiry date, and notification of study closure.

The REB and Research Ethics Office are in support of facilitating the progress of ethical research and thank you in advance for your efforts to protect research participants. Best wishes for a successful project.



Brian J. Murray, MD FRCPC FAAN D, ABSM
Chair, Research Ethics Board
/cap

OR

Lisa Di Prospero, BSc. MSc MRT (T)
Vice-Chair, Research Ethics Board

A-20465.I HRPO Approval Memorandum (Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)

<jessica.l.mendoza19.civ@mail.mil>

Fri 2020-04-03 10:46 AM

To: 'traumatrenholms@Mac.com' <traumatrenholms@Mac.com>

Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (USA) <jodi.h.bennett.civ@mail.mil>; Lorna Very <very@ucalgary.ca>; Gerardo Duque <gerardo.duque@ucalgary.ca>; Robin Smith <robin.smith@ucalgary.ca>; Kevin A. Hildebrand <hildebrk@ucalgary.ca>; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (USA) <kenneth.e.grenier2.civ@mail.mil>; Yadav, Prem CIV USARMY MEDCOM CDMRP (USA) <prem.yadav.civ@mail.mil>; Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA) <kimberly.l.odam.civ@mail.mil>; Kline, Andrea J CIV USARMY MEDCOM USAMRMC (USA) <andrea.j.kline.civ@mail.mil>; Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA) <jessica.l.mendoza19.civ@mail.mil>; Jaldin, Michelle A CTR (USA) <michelle.a.jaldin.ctr@mail.mil>; Frederick, Margaret M CTR USARMY (USA) <margaret.m.frederick.ctr@mail.mil>

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, "PrEvention of post-traumatic joint contractuRes with Ketotifen 2 (PERK 2)," Submitted by J. Andrew I. Trenholm, MD, Queen Elizabeth II Health Sciences Centre (QU2HSC), Halifax, Nova Scotia, Canada, in Support of the Proposal, "PrEvention of Post-Traumatic Joint ContractuRes With Ketotifen 2 (PERK 2)," Submitted by Kevin A. Hildebrand, MD, University of Calgary - Health Research Innovation Centre, Calgary, Alberta, Canada, Project Identification Number 313-2019, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.I

1. The subject protocol (version 5.0 dated 4 October 2019) was approved by the Nova Scotia Health Authority Research Ethics Board on 31 March 2020. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements.
2. The USAMRDC ORP HRPO approved this greater than minimal risk study for the enrollment of 702 subjects across all study sites and 30 subjects at the QE2HSC site.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRDC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. Please note that a Research Monitor (RM) is required to be involved in DOD-supported research studies that are determined to pose more than minimal risk to subjects (DOD Instruction 3216.02, Nov 2011). If the duties of the RM could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the RM is not an agent of the covered entity), your institution may require the identity and location of the RM to be described in the study Health Information Portability and Accountability Act authorization.

5. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to usarmy.detrick.medcom-usamrhc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension or termination of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution (Note: HRPO review and approval of institution is required.), change to the Institutional Review Board (IRB) of Record, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 30 September 2020. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrhc.other.hrpo@mail.mil), by facsimile (301-619-7803), or mail to the U.S. Army Medical Research and Development Command, ATTN: FCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRDC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

6. Please note: The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

7. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

8. The HRPO point of contact for this approval is Margaret M. Frederick, PhD, Human Subjects Protection Scientist, at 301-619-7418, or margaret.m.frederick.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Michelle A. Jaldin, BS, Human Subjects Protection Scientist, at 301-619-6766, DSN 343-6766, or michelle.a.jaldin.ctr@mail.mil.

JESSICA L. MENDOZA, BSN
Human Subjects Protection Scientist and Regulatory Liaison
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Development Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

CLASSIFICATION: UNCLASSIFIED

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)
<jessica.l.mendoza19.civ@mail.mil>
Sent: Tuesday, January 21, 2020 8:23 AM
To: 'Nam, Dr. Diane (Division Of Orthopaedic Surgery)'
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (USA); Lorna Very; Gerardo Duque; Robin Smith; Kevin A. Hildebrand; Milner, Katrine; Kunz, Monica; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (USA); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Kline, Andrea J CIV USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jaldin, Michelle A CTR (USA); Frederick, Margaret M CTR (USA)
Subject: A-20465.j HRPO Approval Memorandum (Project Identification Number 313-2019, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, "PrEvention of post-traumatic joint contractuRes with Ketotifen 2 (PERK 2)," Submitted by Diane Nam, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, in Support of the Proposal, "PrEvention of post-traumatic joint contractuRes with Ketotifen II (PERK II)," Submitted by Kevin A. Hildebrand, MD, University of Calgary – Health Research Innovation Centre, Calgary, Alberta, Canada, Project Identification Number 313-2019, Proposal Log Number OR160026, HRPO Log Number A-20465.j

1. The subject protocol (version 4.0 dated 31 July 2018) was approved by the Sunnybrook Health Sciences Centre (SHSC) Research Ethics Board (REB) on 25 October 2019. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements.
2. The USAMRDC ORP HRPO approved this greater than minimal risk study for the enrollment of 702 subjects across all study sites, and 20 subjects at the SHSC site.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRDC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
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b. A copy of the IRB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the IRB is due no later than 25 October 2020. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

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e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

6. Please note: The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

7. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

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9. The HRPO point of contact for post-approval oversight is Michelle A. Jaldin, BS, Human Subjects Protection Scientist, at 301-619-6766, DSN 343-6766, or michelle.a.jaldin.ctr@mail.mil.

JESSICA L. MENDOZA, BSN
Human Subjects Protection Scientist and Regulatory Liaison
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Development Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

CLASSIFICATION: UNCLASSIFIED

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)

Sent: Monday, January 27, 2020 11:34 AM

To: 'Graham King'

Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (USA); Robin Smith; Lorna Very; Gerardo Duque; 'Katrina.Munro@sjhc.london.on.ca'; Kevin A. Hildebrand; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (USA); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Kline, Andrea J CIV USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jaldin, Michelle A CTR (USA); Frederick, Margaret M CTR (USA)

Subject: A-20465.k HRPO Approval Memorandum (Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, "PrEvention of posttraumatic contractuRes with Ketotifen II (PERK II)," Submitted by Graham J. W. King, MD, St. Joseph Health Care (SJHC), London, Ontario, Canada, in Support of the Proposal, "PrEvention of Post-Traumatic ContractuRes with Ketotifen II (PERK II)," Submitted by Kevin A. Hildebrand, MD, University of Calgary – Health Research Innovation Centre, Calgary, Alberta, Canada, Project ID 111346, Proposal Log Number OR160026, HRPO Log Number A-20465.k

1. The subject protocol (version 4.0 dated 31 July 2018) was approved by the Western University Health Science Research Ethics Board (REB) on 2 October 2019. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements.
2. The USAMRDC ORP HRPO approved this greater than minimal risk study for the enrollment of 702 subjects across all study sites, and 100 subjects at the SJHC site.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRDC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
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c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

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8. The HRPO point of contact for this approval is Margaret M. Frederick, PhD, Human Subjects Protection Scientist, at 301-619-7418, DSN 343-7418, or margaret.m.frederick.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Michelle A. Jaldin, BS, Human Subjects Protection Scientist, at 301-619-6766, DSN 343-6766, or michelle.a.jaldin.ctr@mail.mil.

JESSICA L. MENDOZA, BSN
Human Subjects Protection Scientist and Regulatory Liaison
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Development Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

CLASSIFICATION: UNCLASSIFIED

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)
<jessica.l.mendoza19.civ@mail.mil>
Sent: Monday, November 25, 2019 5:51 AM
To: 'vansurgdoc@gmail.com'
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (USA); Lorna Very; Gerardo Duque; Robin Smith; Kevin A. Hildebrand; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (USA); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jarrett, Raquel T CTR (USA); Anoumatacky-Akessa Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.h - HRPO Approval Memorandum (REB Study Number H17-03529, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, "Prevention of Post-Traumatic Contractures With Ketotifen 2 (PERK 2)," Submitted by Thomas Goetz, MD, University of British Columbia - St Paul's Hospital (UBC), Vancouver, British Columbia, Canada, in Support of the Proposal, "Prevention of Post-Traumatic Contractures With Ketotifen II (PERK II)," Submitted by Kevin A. Hildebrand, MD, University of Calgary - Health Research Innovation Centre, Calgary, Alberta, Canada, REB Study Number H17-03529, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.h

1. The amendment to the subject protocol version 4.0, dated 31 July 2018, was approved by the Providence Health Care Research Ethics Board (REB) on 30 October 2019. The U.S. Army Medical Research and Development Command (USAMRDC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed the protocol and found that it complies with applicable DOD, U.S. Army, and USAMRDC human subjects protection requirements.
2. The USAMRDC ORP HRPO approved this greater than minimal risk study for the enrollment of 30 subjects.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRDC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. Please note that a Research Monitor (RM) is required to be involved in DOD-supported research studies that are determined to pose more than minimal risk to subjects (DOD Instruction 3216.02, Nov 2011). If the duties of the RM could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the RM is not an agent of the covered entity), your institution may require the identity and location of the RM to be described in the study Health Information Portability and Accountability Act authorization.

5. The Principal Investigator must provide the following post-approval submissions to the HRPO via email to usarmy.detrick.medcom-usamrmc.other.hrpo-cr-documents@mail.mil. Failure to comply could result in suspension or termination of funding.

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRDC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution (Note: HRPO review and approval of institution is required.), change to the REB of Record, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the REB continuing review approval letter must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the REB is due no later than 2 July 2020. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

c. The final study report submitted to the REB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), by facsimile (301-619-7803), or mail to the U.S. Army Medical Research and Development Command, ATTN: FCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the REB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or REB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRDC ORP HRPO. The report must include actions taken by the institution and the REB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

6. **Please note:** The USAMRDC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRDC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

7. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

8. The HRPO point of contact for this approval is Ismael Anoumatacky-Akessa Pokou, DDS, Human Subjects Protection Scientist,

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist,

JESSICA L. MENDOZA, BSN, CCRC
Human Subjects Protection Scientist and Regulatory Liaison
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Development Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

CLASSIFICATION: UNCLASSIFIED

CLASSIFICATION: UNCLASSIFIED

A Study Details:

Protocol #:	PERK2_KAH	Date:	11222019
Order # (if applicable):	1	Sponsor:	Dr. Kevin Hildebrand

B Receiver Details:

Name of Site (Centre Code):	The Ottawa Hospital, Civic Campus
Requesting Individual:	Sherry Weir
Department / Attention:	Pharmacy Department, Room CS06-1
Address Line 1:	1053 Carling Avenue,
Address Line 2:	Ottawa, ON
Address Line 3:	Canada
Postal Code:	K1Y 4E9
Telephone:	
Email:	

C Items Requisitioned:

Material Name	Strength	Quantity and unit of measure
Example: Product ABC	10mg	75 x 100ml
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit

List Specific Treatment Numbers (an additional list may be attached to this document):

Treatment # List	Treatment # List	Treatment # List	Treatment # List	Treatment # List	Treatment # List

D Date Required:

Date Required:	Click or tap to enter a date.
Temperature Range:	Requesting Individual.

EMAIL COMPLETED FORM TO barl@barl.ca

Cold Chain Orders Ship Day: MONDAY, TUESDAY, or WEDNESDAY by 15:00 EST.

Ambient Temperature Orders Ship Days: MONDAY, TUESDAY, WEDNESDAY or THURSDAY by 15:00 EST.

If Order not received within 2 business days from date of order, contact:

A Study Details:

Protocol #:	PERK2_KAH	Date:	11222019
Order # (if applicable):	1	Sponsor:	Dr. Kevin Hildebrand

B Receiver Details:

Name of Site (Centre Code):	The Ottawa Hospital, General Campus
Requesting Individual:	Wendy Aikens / Susan Fetzer
Department / Attention:	Pharmacy Department, Clinical Trials – Room M1550
Address Line 1:	501 Smyth Road,
Address Line 2:	Ottawa, ON
Address Line 3:	Canada
Postal Code:	K1H 8L6
Telephone:	
Email:	

C Items Requisitioned:

Material Name	Strength	Quantity and unit of measure
Example: Product ABC	10mg	75 x 100ml
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit

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Date Required:	Click or tap to enter a date.
Temperature Range:	Requesting Individual.

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Ambient Temperature Orders Ship Days: MONDAY, TUESDAY, WEDNESDAY or THURSDAY by 15:00 EST.

If Order not received within 2 business days from date of order, contact:

A Study Details:

Protocol #:	PERK2_KAH	Date:	12182019
Order # (if applicable):	1	Sponsor:	Dr. Kevin Hildebrand

B Receiver Details:

Name of Site (Centre Code):	University of Vermont Medical Center
Requesting Individual:	Marcia Dunham, R.Ph.
Department / Attention:	Pharmacy Investigational Drug Service (Attn: Jill Rockwood)
Address Line 1:	111 Colchester Ave.
Address Line 2:	Burlington, VT
Address Line 3:	USA
Postal Code:	05401
Telephone:	
Email:	

C Items Requisitioned:

Material Name	Strength	Quantity and unit of measure
Example: Product ABC	10mg	75 x 100ml
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit

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D Date Required:

Date Required:	Click or tap to enter a date.
Temperature Range:	Requesting Individual.

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Ambient Temperature Orders Ship Days: MONDAY, TUESDAY, WEDNESDAY or THURSDAY by 15:00 EST.

If Order not received within 2 business days from date of order, contact:

A Study Details:

Protocol #:	PERK2_KAH	Date:	02072020
Order # (if applicable):	1	Sponsor:	Dr. Kevin Hildebrand

B Receiver Details:

Name of Site (Centre Code):	St. Paul's Hospital, PHC
Requesting Individual:	Caroline Briggs, BSc. Pharm, ACPR
Department / Attention:	Pharmacy Department
Address Line 1:	Rm 162R-1081 Burrard Street
Address Line 2:	Vancouver, B.C.
Address Line 3:	Canada
Postal Code:	V6Z 1Y6
Telephone:	
Email:	

C Items Requisitioned:

Material Name	Strength	Quantity and unit of measure
Example: Product ABC	10mg	75 x 100ml
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit

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Treatment # List	Treatment # List	Treatment # List	Treatment # List	Treatment # List	Treatment # List

D Date Required:

Date Required:	Click or tap to enter a date.
Temperature Range:	Requesting Individual.

EMAIL COMPLETED FORM TO barl@barl.ca

Cold Chain Orders Ship Day: MONDAY, TUESDAY, or WEDNESDAY by 15:00 EST.

Ambient Temperature Orders Ship Days: MONDAY, TUESDAY, WEDNESDAY or THURSDAY by 15:00 EST.

If Order not received within 2 business days from date of order, contact:

A Study Details:

Protocol #:	PERK2_KAH	Date:	03032020
Order # (if applicable):	1	Sponsor:	Dr. Kevin Hildebrand

B Receiver Details:

Name of Site (Centre Code):	St. Joseph's Hospital
Requesting Individual:	Leanne Vanderhaeghe
Department / Attention:	Pharmacy
Address Line 1:	Pharmacy – Room #A0-011
Address Line 2:	268 Grosvenor St.
Address Line 3:	London, Ontario, Canada
Postal Code:	N6A 4V2
Telephone:	
Email:	

C Items Requisitioned:

Material Name	Strength	Quantity and unit of measure
Example: Product ABC	10mg	75 x 100ml
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit
Material Name	strength.	Quantity and unit

List Specific Treatment Numbers (an additional list may be attached to this document):

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D Date Required:

Date Required:	Click or tap to enter a date.
Temperature Range:	Requesting Individual.

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Ambient Temperature Orders Ship Days: MONDAY, TUESDAY, WEDNESDAY or THURSDAY by 15:00 EST.

If Order not received within 2 business days from date of order, contact:

25 November 2019

Dr. Steve Papp, Qualified Investigators
The Ottawa Hospital, Civic Campus
1053 Carling Ave
Ottawa, ON K1Y 4E9

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Papp:

This letter is in follow-up to my recent Site Initiation Visit performed on November 19/20, 2019. The initiation visit included review of the following:

- Study Protocol/Trial Manual
- Pharmacy Dispensing and Destruction Procedures
- Participant Recruitment Procedures
- Informed Consent Procedures
- Blood Pregnancy Testing Procedures
- Participant Screening & Randomization
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- Drug Tracking System (DTS)
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	Response
Who do we screen for?	All elbow fractures and/or dislocations. Screen fails occur thereafter based on inclusion and exclusion criteria (i.e. if patient is non-operative)
Patients would be randomized ~10 days before surgery. How will we address 2 week follow up visit if it is 2 weeks post-operation?	All 2 week post-randomization data may be collected via phone call aside from ROM and weight measurements. Schedule of Events: Day 0: Randomize participant Day ~10: Surgery Day 14 ($\pm$ 3 days): Phone call Day 28-35: Interim visit (optional) Day 42: 6 week follow-up visit

We are pleased to announce that your site is now **approved to enroll** as of the date you receive trial medication.

We will be in touch for any future trial medication requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the **first on-site monitor session** after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
Radiographs	Inquire about having oblique (internal and external) views to be captured at each visit	Nicole Harris / Dr. Papp
Training and Delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion	Nicole Harris
Pharmacy	Walk through pharmacy following drug arrival to ensure 18 bottles have arrived and are stored in temperature controlled space	Nicole Harris

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,



Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone

25 November 2019

Dr. J Pollock, Qualified Investigators
The Ottawa Hospital, General Campus
501 Smyth Rd, Ottawa
ON K1H 8L6

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Pollock:

This letter is in follow-up to my recent Site Initiation Visit performed on November 19/20, 2019. The initiation visit included review of the following:

- Study Protocol/Trial Manual
- Pharmacy Dispensing and Destruction Procedures
- Participant Recruitment Procedures
- Informed Consent Procedures
- Blood Pregnancy Testing Procedures
- Participant Screening & Randomization
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- Drug Tracking System (DTS)
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	Response
Who do we screen for?	All elbow fractures and/or dislocations. Screen fails occur thereafter based on inclusion and exclusion criteria (i.e. if patient is non-operative)
Patients would be randomized ~10 days pre-operative. How will we address 2 week follow up visit if it is 2 weeks post-operation?	All 2 week post-randomization data may be collected via phone call aside from ROM and weight measurements. Schedule of Events: Day 0: Randomize participant Day ~10: Surgery Day 14 ($\pm$ 3 days): Phone call Day 28-35: Interim visit (optional) Day 42: 6 week follow-up visit

We are pleased to announce that your site is now **approved to enroll** as of the date you receive trial medication.

We will be in touch for any future trial medication requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the **first on-site monitor session** after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
Urine Pregnancy Test	Identify process for obtaining urine pregnancy test after consenting and before randomization	Katie McIlquham
Radiographs	Inquire about having oblique (internal and external) views to be captured at each visit	Katie McIlquham / Dr. Pollock
Training and Delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion	Katie McIlquham
Pharmacy	Walk through pharmacy following drug arrival to ensure 18 bottles have arrived and are stored in temperature controlled space	Katie McIlquham

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,



Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone

11 December 2019

Dr. Benoit, Qualified Investigators
UVM Medical Center
111 Colchester Ave,
Burlington, VT 05401 USA

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Benoit:

This letter is in follow-up to my recent Site Initiation Visit performed on November 19/20, 2019. The initiation visit included review of the following:

- Study Protocol/Trial Manual
- Pharmacy Dispensing and Destruction Procedures
- Participant Recruitment Procedures
- Informed Consent Procedures
- Blood Pregnancy Testing Procedures
- Participant Screening & Randomization
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	Response
When can surgery occur?	Surgery can occur before or after randomization. Randomization must occur within 7 days of injury.
Does the REDCap randomization form need to be completed prior to providing medication to consented participant?	You will be required to populate all information except the “instructions given” and “date & time of first dose administration” prior to sending medication request to pharmacy and dispensing the medication to participant.
How will documents be sent to sites?	We will allow your site to decide if you would prefer email updates on new documents to be approved by your local IRB and/or to add you to our updated PERK 2 Dropbox.

We are pleased to announce that your site is now **approved to enroll** as of the date you receive trial medication.

We will be in touch for any future trial medication requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the **first on-site monitor session** after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
Urine pregnancy testing	Identify hospitals standard of care procedures for urine pregnancy testing.	Melissa Cuke
Range of motion testing	Practice the ROM measurements (elbow extension and flexion, and forearm supination and pronation).	Melissa Cuke
IRB reporting	Check in with local IRB about reporting requirements for AE, SAE, and protocol violations.	Melissa Cuke
Training and delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion.	Melissa Cuke
Pharmacy	Walk through pharmacy following drug arrival to ensure 18 bottles have arrived and are stored in temperature controlled space.	Melissa Cuke

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,



Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone

Dr. Goetz, Qualified Investigator
St. Paul's Hospital
1081 Burrard St,
Vancouver, BC V6Z 1Y6

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Goetz & team:

This letter is in follow-up to my recent Site Initiation Visit performed on December 16 and December 18, 2019. The initiation visit included review of the following:

- Study Protocol/Trial Manual
- Participant Recruitment Procedures
- Informed Consent Procedures
- Urine Pregnancy Testing Procedures
- Participant Screening & Randomization
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- Pharmacy Dispensing and Destruction Procedures
- Drug Tracking System
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	Response
Can trial medication be taken prior to surgery?	If participant is randomized pre-operatively, ensure you talk to the participants' healthcare team (nurse and/or treating surgeon) to ask about providing this medication with a small amount of water before surgery. If this is a problem, the participant can start trial medication post-operatively instead.
Can we send an email to the participants if they cannot be reached via phone call/prefer emails at 1-, 3-, 4-, and 5- weeks?	Yes, as long as all questions from the Case Report Forms are asked and you receive a response.
Do we keep trial medication bottles at Pharmacy for trial monitor to check at her visit?	No, these bottles may be disposed of following Pharmacy SOP's as soon as returned to clinic at 6 week visit.
Why is oral hypoglycemic medication an exclusionary criteria for the trial?	Thrombocytopenia has been reported when taking oral hypoglycemic medication with Ketotifen Fumarate.

Can the patient use an insulin patch?	Yes
Why are both severe renal and hepatic impairment both exclusionary criteria for the trial?	Both the liver and kidneys function to metabolize any drug within the body. Patients with severe impairments should not be taking trial medication based on this.

We are pleased to announce that your site is now **approved to enroll** as of the date you receive trial medication.

We will be in touch for any future trial medication requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the **first on-site monitor session** after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
Urine pregnancy testing	Identify hospitals standard of care procedures for urine pregnancy testing.	Zafeiria Glaris
REB reporting	Check in with local IRB about reporting requirements for AE, SAE, and protocol violations.	Zafeiria Glaris
Training and delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion.	Zafeiria Glaris
Pharmacy	Walk through pharmacy following drug arrival to ensure 18 bottles have arrived and are stored in temperature controlled space.	Zafeiria Glaris and Caroline Briggs

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,

A handwritten signature in black ink, appearing to read 'KHil', is positioned above the printed name.

Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone

Dr. King, Qualified Investigator
St. Joseph's Hospital
30 The Queensway,
Toronto, ON M6R 1B5

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Graham King & team:

This letter is in follow-up to my recent Site Initiation Visit performed on February 25, 2020. The initiation visit included review of the following:

- Study Protocol/Trial Manual
- Participant Recruitment Procedures
- Informed Consent Procedures
- Urine Pregnancy Testing Procedures
- Participant Screening & Randomization
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- Pharmacy Dispensing and Destruction Procedures
- Drug Tracking System
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Questions	Responses
What is bony deformation adverse event?	Bony Deformation is a posttraumatic bone abnormality from healing in a deformed position after fracture occurred.
Does surgery have to occur within 7 days?	No, randomization must take place within 7 days of injury. However surgery can take place outside of this 7 day window.
What happens if patient verbally states they are not pregnant and do not require a pregnancy test?	For the PERK 2 Trial we will require a pregnancy test for all women who are of child-bearing age (up until 2 years post-menopausal). This is kept on file as source document verification.
Can the local site train all other staff after initial SIV?	Yes, after initial SIV both Dr. King and Katrina can perform training to the delegated qualified investigators and other research staff on the team. Any new trained staff will need to be added to the training and delegation logs.

Ambient monitoring of temperatures are tested 24/7 in pharmacy. Can this be used rather than a daily max/min temperature device?	Yes, as long as a report is filed in the PERK 2 pharmacy binder that reflects the daily temperatures.
When can the site expect access to the system?	Once the shipment of the drug has been made, the Coordinating Centre will be sending an email to the site. When trial medication arrives to site (mid-March), access to REDCap and Drug Tracking System will be provided to the site via email.
When are we ready to start recruitment?	The PERK 2 trial medication is scheduled for shipment ASAP and will take about 2-3 weeks before arrival. Following arrival at the site, the Pharmacist must confirm drug status and set to “available” in Drug Tracking System. Once complete, recruitment can take place.

We are pleased to announce that your site is now **approved to enroll** as of the date you receive trial medication.

We will be in touch for any future trial medication requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the **first on-site monitor session** after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
REB reporting	Check in with local IRB about reporting requirements for AE, SAE, and protocol violations.	Katrina Munro
Training and delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion.	Katrina Munro
Pharmacy	Walk through pharmacy following drug arrival to ensure 18 bottles have arrived and are stored in temperature controlled space.	Katrina Munro & Leanne Vanderhaeghe

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,

A handwritten signature in black ink, appearing to read 'KHil', is positioned above the printed name.

Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone



11 March 2020

Dr. Michael Bosse, Qualified Investigator
Carolinas Medical Centre (Site #6)
1000 Blythe Blvd,
Charlotte, NC 28203, USA

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Bosse,

This letter is in follow-up to my recent Site Initiation Visit performed on March 11, 2020. The initiation visit included review of the following:

- Study Personnel and Facilities
- Study Protocol
- Pharmacy
- Subject Recruitment Procedures
- Informed Consent Procedures
- Urine Pregnancy Testing Procedures
- Participant Screening & Enrollment Logs
- Case Report Forms
- Electronic Data Capture System (REDCap)
- Drug Tracking System (IWRS)
- (Serious) Adverse Event Reporting

The following are responses to questions raised during the visit:

Question	Response
Do we require to collect participant initials on every page of our ICF if that is not required by the local IRB?	No, for your site you do not require this.
Can the lead site supply the pregnancy tests?	No, each site can use their start-up funds to purchase pregnancy tests. At our site we used the ER tests
How do we explain to the patients WHY they require using 2 methods of contraception	Based on the unknown teratogenic effects of a growing fetus, Health Canada has enforced this
What are the requirements of post-operative x-rays?	All 4 views are required at all visits (pre- and post-operative, 2-, 6-, 12-, 24-, and 54-weeks)

	Depending on standard of care, some views may not be collected during pre- and post-operation. Please let the lead site know if this is the case. The 24- and 52-week follow up may not require any views if the fracture is united (determined by treating surgeon).
What is the next step after the SIV?	After completion of SIV training, we will organize the drug to be shipped to your site. Drug processing and shipment will occur after we have receive approval from your sites' research pharmacist.

We are pleased to announce that your site is now **approved to enroll** as of March 11, 2020.

We will be in touch for any future drug requirements, SAE reporting, and any questions or concerns about the PERK 2 Trial.

We would like to schedule the first monitor session with Jackie Busheikin after 3 participants are successfully randomized into the PERK 2 Trial.

I would like to thank you on behalf of our PERK 2 Team for your participation in this clinic trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,



Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
 PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
 Professor, Department of Surgery
 University of Calgary and Alberta Health Services – Calgary Zone

April 22nd, 2020

Dr. Diane Nam, Qualified Investigator
Sunnybrook Health Science Centre
2075 Bayview Avenue, Rm D514,
Toronto, Ontario, Canada
M4N 3M5

Subject: Site Initiation Visit Follow-Up for PERK 2 Trial

Dear Dr. Nam:

This letter is a follow-up to my recent Site Initiation Visit performed on March 25th, 2020 and April 22nd, 2020. The initiation visit included review of the following:

- Study Personnel and Facilities
- Study Protocol/Trial Manual
- Pharmacy Procedures
- Subject Recruitment Procedures
- Informed Consent Procedures
- Urine/Blood Serum Pregnancy Testing Procedures
- Participant Screening & Enrollment Logs
- Case Report Forms/Source Documentation
- Electronic Data Capture System (REDCap)
- Drug Tracking System (IWRS)
- (Serious) Adverse Event Reporting and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	Response
If patient does not take hypoglycemic medication but does get insulin shots, would they be excluded? Is it the medication or being diagnosed with diabetes?	They would not be excluded. Patient is allowed to take insulin. The concern is in the interaction between hypoglycemic medications and ketotifen fumarate (IP).
What should be done if surgeon decides elbow needs to be immobilized for 21 days after surgery, but participant is already taking IP?	Ultimately, it is the surgeons decision. A conversation can be started between the site and sponsor to attempt early mobilization. However, if plan is still to immobilize, a

	protocol violation would be completed and participant withdrawn for failing the screen.
What if the surgery is scheduled for a later time (i.e. closer to 2 week or 6 week follow up visit) that conflicts with post randomization/first dose schedule?	Participant would continue to attend scheduled visits as most data could be gathered. Range of motion will probably not gathered, so a query would be started to explain what is occurring with the surgery schedule.
Surgeon's may prescribe antihistamines with Percocet after surgery (i.e. skin itchiness). While taking IP, they should not be taking any other antihistamines? Why?	No antihistamines can be taken while under IP. We are concerned with excessive sedation/drowsiness from the antihistamine. Dr. Hildebrand is available to discuss with surgeon, if needed.
Can PROM's be emailed to participant without having to add email to REDcap? REB does not let us keep any personal contact information within REDcap.	Yes. REDcap provides an area called "Survey Options" at the top of the PROM's. Once you access this platform, you can address the questionnaire to any email they prefer without keeping their personal contact information within the REDcap system.

We will be in touch in the future to begin the next processes for study startup, including the allocation of drug, database access and addressing any questions or concerns about the trial.

We would like to schedule the first monitor session with Jackie Busheikin after 3-5 participants are successfully randomized into the PERK 2 Trial.

Action items to address:

Finding	Action Required	Assigned To
Training and Delegation logs	A copy of the signed training and delegation logs to be sent to coordinating centre following completion.	Monica Kunz
IP Storage and Log procedures	Identify storage procedures to be followed at site, if IP will be stored with coordinator and not at pharmacy.	Monica Kunz/Katrine Milner



I would like to thank you on behalf of our PERK 2 Team for your participation in this clinical trial and I look forward to working with you and your study team. Please feel free to contact me if you have any additional questions or concerns.

Thank you for your continued support of the **PERK 2 Trial!**

Sincerely,

A handwritten signature in black ink, appearing to read "K. Hildebrand".

Dr. Kevin A. Hildebrand, MD, FRCSC, CCPE
PERK 2 Sponsor and Primary Investigator, Peter Lougheed Centre
Professor, Department of Surgery
University of Calgary and Alberta Health Services – Calgary Zone

PERK 2 PID 4227

Data Exports, Reports, and Stats

Randomized Subjects

Table not displaying properly. [?](#)

Screening ID screen_id	Event Name redcap_event_name	Repeat Instrument redcap_repeat_instrument	Repeat Instance redcap_repeat_instance	Data Access Group redcap_data_access_group	BOTTLE ID rand_group	Date of randomization rand_dt
5358-4 (Participant ID 01-001)	Screening/Randomization			Peter Lougheed Centre	10008	2019-06-29
5362-2 (Participant ID 05-001)	Screening/Randomization			South Health Campus	10072	2019-07-02
5362-13 (Participant ID 05-002)	Screening/Randomization			South Health Campus	10049	2019-07-26
5358-5 (Participant ID 01-002)	Screening/Randomization			Peter Lougheed Centre	10001	2019-07-27
5358-47 (Participant ID 01-003)	Screening/Randomization			Peter Lougheed Centre	10006	2019-08-29
5362-31 (Participant ID 05-003)	Screening/Randomization			South Health Campus	10073	2019-09-03
5362-34 (Participant ID 05-004)	Screening/Randomization			South Health Campus	10066	2019-09-04
5358-56 (Participant ID 01-004)	Screening/Randomization			Peter Lougheed Centre	10020	2019-09-11
5362-39 (Participant ID 05-005)	Screening/Randomization			South Health Campus	10050	2019-09-17
5358-70 (Participant ID 01-005)	Screening/Randomization			Peter Lougheed Centre	10012	2019-10-11
5362-46 (Participant ID 05-006)	Screening/Randomization			South Health Campus	10068	2019-10-15
5370-1 (Participant ID 13-001)	Screening/Randomization			Sturgeon Community Hospital	10113	2019-10-16
5370-3 (Participant ID 13-002)	Screening/Randomization			Sturgeon Community Hospital	10107	2019-10-28
5370-4 (Participant ID 13-003)	Screening/Randomization			Sturgeon Community Hospital	10101	2019-10-29
5362-56 (Participant ID 05-007)	Screening/Randomization			South Health Campus	10053	2019-11-05
5358-77 (Participant ID 01-006)	Screening/Randomization			Peter Lougheed Centre	10009	2019-11-08
5370-6 (Participant ID 13-004)	Screening/Randomization			Sturgeon Community Hospital	10102	2019-11-20
5358-87 (Participant ID 01-007)	Screening/Randomization			Peter Lougheed Centre	10011	2019-11-29
5370-8 (Participant ID 13-005)	Screening/Randomization			Sturgeon Community Hospital	10108	2019-12-04
5360-1 (Participant ID 03-001)	Screening/Randomization			Foothills Medical Centre	10037	2019-12-06
5360-3 (Participant ID 03-002)	Screening/Randomization			Foothills Medical Centre	10036	2019-12-09
5362-71 (Participant ID 05-008)	Screening/Randomization			South Health Campus	10070	2019-12-10
5362-72 (Participant ID 05-009)	Screening/Randomization			South Health Campus	10079	2019-12-10
5358-93 (Participant ID 01-008)	Screening/Randomization			Peter Lougheed Centre	10030	2019-12-20
5360-5 (Participant ID 03-003)	Screening/Randomization			Foothills Medical Centre	10028	2019-12-23

Screening ID screen_id	Event Name redcap_event_name	Repeat Instrument redcap_repeat_instrument	Repeat Instance redcap_repeat_instance	Data Access Group redcap_data_access_group	BOTTLE ID rand_group	Date of randomization rand_dt
5362-81 (Participant ID 05-010)	Screening/Randomization			South Health Campus	10056	2019-12-26
5368-1 (Participant ID 11-001)	Screening/Randomization			The Ottawa Hospital, Civic Campus	10155	2020-01-10
5358-103 (Participant ID 01-009)	Screening/Randomization			Peter Lougheed Centre	10203	2020-01-23
5358-104 (Participant ID 01-010)	Screening/Randomization			Peter Lougheed Centre	10197	2020-01-24
5362-92 (Participant ID 05-011)	Screening/Randomization			South Health Campus	10233	2020-01-27
5362-94 (Participant ID 05-012)	Screening/Randomization			South Health Campus	10239	2020-02-04
5360-10 (Participant ID 03-004)	Screening/Randomization			Foothills Medical Centre	10219	2020-02-05
5359-10 (Participant ID 02-001)	Screening/Randomization			University of Maryland Medical Center	10131	2020-02-07
5369-1 (Participant ID 12-001)	Screening/Randomization			The Ottawa Hospital, General Campus	10185	2020-02-11
5360-12 (Participant ID 03-005)	Screening/Randomization			Foothills Medical Centre	10209	2020-02-12
5370-11 (Participant ID 13-006)	Screening/Randomization			Sturgeon Community Hospital	10103	2020-02-17
5370-12 (Participant ID 13-007)	Screening/Randomization			Sturgeon Community Hospital	10114	2020-02-21
5374-1 (Participant ID 17-001)	Screening/Randomization			University of Vermont Medical Center	10245	2020-02-27
5358-120 (Participant ID 01-011)	Screening/Randomization			Peter Lougheed Centre	10204	2020-03-02
5362-104 (Participant ID 05-013)	Screening/Randomization			South Health Campus	10227	2020-03-02
5359-14 (Participant ID 02-002)	Screening/Randomization			University of Maryland Medical Center	10125	2020-03-03
5358-122 (Participant ID 01-012)	Screening/Randomization			Peter Lougheed Centre	10198	2020-03-05
5358-125 (Participant ID 01-013)	Screening/Randomization			Peter Lougheed Centre	10191	2020-03-12
5374-2 (Participant ID 17-002)	Screening/Randomization			University of Vermont Medical Center	10251	2020-03-16
5358-126 (Participant ID 01-014)	Screening/Randomization			Peter Lougheed Centre	10192	2020-06-30
5362-108 (Participant ID 05-014)	Screening/Randomization			South Health Campus	10234	2020-07-17
5374-3 (Participant ID 17-003)	Screening/Randomization			University of Vermont Medical Center	10257	2020-07-27
5368-16 (Participant ID 11-002)	Screening/Randomization			The Ottawa Hospital, Civic Campus	10166	2020-08-20
5369-10 (Participant ID 12-002)	Screening/Randomization			The Ottawa Hospital, General Campus	10186	2020-09-22
5369-11 (Participant ID 12-003)	Screening/Randomization			The Ottawa Hospital, General Campus	10173	2020-10-01
5358-141 (Participant ID 01-015)	Screening/Randomization			Peter Lougheed Centre	10193	2020-10-02

CONTENT	DETAIL
Introduction Name of trial plus (ClinicalTrials.gov number) Study Sponsor / Principal Investigator Funding Agency Objectives of trial, including interventions being investigated Outline of scope of charter	Prevention of posttraumatic contractures with Ketotifen 2 – PERK 2 (NCT03582176) University of Calgary / Kevin A. Hildebrand US Department of Defense – Congressionally Directed Medical Research Programs Primary Objective: To determine if Ketotifen given within 7 days of injury can reduce post-traumatic elbow joint contractures when compared to placebo. Secondary Objectives: 1) To ascertain the optimal dose of Ketotifen and 2) to compare adverse events in Ketotifen and placebo groups. (See Figure 1) The purpose of this document is to describe the roles and responsibilities of the Data Monitoring Committee (DMC) for the PERK 2 trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.
Before agreeing to be part of the DMC	All potential DMC members will have sight of the protocol/outline before agreeing to join the committee. Before recruitment began the trial had undergone peer review by the US Department of Defense, internal; review, and scrutiny by the site Institutional Review Boards (IRB), Office of Human Research Protections (OHRP), US Food and Drug Administration (FDA), Health Canada (HC), Trial Management Group (TMG) and Trial Steering Committee (TSC). Therefore, if a potential DMC member has major reservations about the trial, they should report these to the TSC and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Roles and responsibilities A broad statement of the aims of the committee Terms of reference	To safeguard the interests of trial's participants, potential participants, investigators and sponsor; to assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct, and protect its validity and credibility. The DMC should review the progress of this trial and provide appropriate advice on the conduct of the trial to the Trial Steering Committee (TSC).

CONTENT	DETAIL
Specific roles of DMC 1. To meet via tele/video conference yearly to undertake an interim review of the trials progress. 2. To meet via tele/videoconference to review serious adverse events (SAEs) when deemed necessary by the Principal Investigator or the Trial Steering Committee (TSC)- see Appendix 2 for stopping details. 3. To undertake a formal review of the trial at the half-way point of recruitment.	To undertake interim review of the trial's progress by: • assessing data quality, including completeness (thereby encouraging collection of high-quality data) • monitoring recruitment figures and losses to follow-up • monitoring compliance with the protocol by participants and investigators • monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered • monitoring evidence for treatment harm e.g. toxicity, SAE's, deaths • recommending whether the trial should continue to recruit or follow-up [see section on decision-making] • recommending any major changes to the protocol, where necessary (e.g. changes to the recruitment procedures, inclusion criteria, endpoints, data collection, etc.) • advising on and/or endorsing any major protocol modifications suggested by investigators or sponsors (e.g. changes to the inclusion criteria, endpoints, data collection, etc) • monitoring planned sample size with regards (i) <i>a priori</i> assumptions about the control arm outcome and (ii) emerging differences in clinically relevant subgroups • suggest additional data analyses • assessing the impact and relevance of any external evidence provided • monitoring compliance with previous DMC recommendations • considering the ethical implications of any recommendations made by the DMC The DMC should not have a role in increasing or decreasing the planned sample size as it is not blind to the current results of the trial. (See decision-making)
Whether the DMC will meet before the start of the trial	The DMC should meet early in to the trial. The timing should within one year of commencing accrual or before 10% (70 participants) of the calculated sample size; whichever is sooner. The aim of the first meeting would be to discuss the working of the DMC, to confirm the nominated chair and create a first report. The first report should contain tables and graphs based on the available real data, to familiarise the DMC members with the format that will be used in this and subsequent reports and to give them the opportunity to suggest changes and additions.

CONTENT	DETAIL
Any specific regulatory issues	A No Objection Letter (NOL) from HC (Control number 218219) and Investigational New Drug (IND) approval from the FDA (IND 136411) to use Ketotifen for prevention of Post-traumatic Joint Contractures
Whether members of the DMC will have a contract	DMC members will agree to this document to register their assent. This can be in the form of a letter or email and should confirm (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter. There will be no formal contracts.
Composition Membership and size of the DMC	The membership will consist of a minimum of 3 individuals that includes at least one clinician and at least one statistician. Members have been chosen because they are experienced in trials and/or the disease area. The members will be recommended and approved by the TSC. The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some involvement that could impact on the trial). Members should not serve on DMCs of similar, concurrently active trials as this could compromise the independence of the trial and possibly the confidentiality of the results of the individual trials. Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members (Appendix 1). <u>Note:</u> “Competing interests” is the preferred term over “conflicts of interest” because it avoids any implication of wrongdoing and may encourage greater co-operation in reporting interests (Reference: Br J Med). The members of the DMC for PERK 2 are: (1) Name (Clinician), Town (2) Name (Clinician), Town (3) Name (Statistician), Town (4) Name (Clinician), Town
The chair, how they are chosen and the chair’s role. (Likewise, if relevant, the vice-chairman)	The TSC will nominate the chair. The chair is (<u>TBA</u>), a clinician serving on the DMC. The Chair is expected to facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a statistician to provide independent statistical expertise and to further guide the other DMC members through the report. The DMC statistician is not expected to prepare the DMC report.

CONTENT	DETAIL
The responsibilities of the trial statistician The responsibilities of the trial office team The responsibilities of the PI and other members of the TMG	The trial statistician is Tolulope Sajobi. He is responsible for the production of the report to the DMC, will guide the DMC through the report, may participate in DMC discussions, and may have to take notes on some occasions. The trial office team (i.e. Gerardo Duque, Trial Manager; Ayoola Ademola, PhD candidate Biostatistician) will input non-confidential sections of the DMC report. The PI, Kevin A. Hildebrand, may be asked and should be available to attend open sessions of the DMC meeting. The other TSC members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).
Relationships Relationships with Principal Investigator, the Trial Steering Committee (TSC) and/or the sponsor and regulatory bodies Clarification of whether the DMC are advisory (make recommendations) or executive (make decisions) Any payments to DMC members The need for DMC members to disclose information about any competing interests	The responsibilities of the other trial committees are presented in the protocol. Figure 2 presents the relationship of the DMC to other the other trial committees. The DMC is advisory to the TSC. The TSC is the executive body for the trial. Members should be reimbursed for any reasonable travel, accommodation or other costs (e.g. telephone) incurred. The trial office team does not expect to pay DMC members or their employers. Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. Most competing interests are acceptable if disclosed (see Appendix 1). DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
Organisation of DMC meetings Expected frequency of DMC meetings Whether meetings will be face-to-face or by teleconference	It is recommended that the DMC meet at least yearly and will otherwise depend on the wishes of the DMC and needs of the trial office will be considered when planning each meeting. The meetings will be conducted by teleconference or videoconference where possible. The PI, Kevin Hildebrand, will participate if the DMC requests his presence. Arrangements have been made for an early meeting, before many main outcome measure events have been accrued. This gives a “test run” for the DMC decision-making process and a test run for trial office team report production.

CONTENT	DETAIL
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Definitions <u>Closed session:</u> Only DMC members, and the trial statistician (Tolulope Sajobi) should be present in closed sessions. Sessions attended only by DMC members may be referred to as executive sessions. <u>Open session:</u> Attended by those at the closed session, plus the PI(s), chair of the TSC and if deemed necessary representatives of the sponsor, funder, or regulator. Those attending the open session may attend via videoconference or, if appropriate by phone. The format will be: 1 Closed session: All parts of the report are discussed, and DMC discussion ($\pm$ trial statistician at discretion of DMC) 2 Open session: Discussion with other attendees on any matters arising from the closed session. (this assumes that others will have read the “open” report in advance)
Trial documentation and procedures to ensure confidentiality and proper communication Intended content of material to be available in open sessions Intended content of material to be available in closed sessions Will the DMC be blinded to the treatment allocation? Who will see the accumulating data and interim analysis? Who will be responsible for identifying and circulating external evidence (e.g. from other trials/ systematic reviews) To whom the DMC will communicate the decisions/recommendations that are reached	<u>Open sessions:</u> Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance). AE/SAE details based on pooled data may be presented, although this may be presented by arm if AE/SAE are not the primary outcome measure, at the discretion of the DMC. <u>Closed sessions:</u> In addition to all the material available in the open session, the closed session material would usually include efficacy and safety data by treatment group. The DMC will be blinded to the identity of the treatment arms, except in situations where the safety of patients would otherwise be compromised. Interim data and analyses by treatment group (and the deliberations of the DMC) should be available only to those present in the closed sessions i.e. only members of the DMC and the trial statistician. DMC members must not share confidential information with people outside the DMC, including the PI. Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the DMC members. The PI (maybe the TMG, as a whole) and the trial office team will collate any such information. The DMC will report its recommendations in writing to the TSC. This should be copied to the trial statistician (or trial manager) and should be sent via the trial office team to coincide with TSC

It is advised that the sample size is not revised on the basis of the treatment effect at an interim analysis. This is because the type I error and power would have to be recalculated on the basis of the correlation between the observed estimate of the treatment effect and the final target estimate. The problem arises because the correlation is not clear at this interim design stage. It is analogous to the problems of interim looks at the data but is more difficult to assess because we are dealing with estimation.

CONTENT	DETAIL
When the DMC is quorate for decision-making	Effort should be made for all members to attend. The trial office team will try to ensure that a date is chosen to enable attendance of all members. Members who cannot via videoconference should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as soon after the meeting as possible to check, they agree. If they do not, a further videoconference or teleconference should be arranged with the full DMC.
Reporting To whom the DMC will report their recommendations/decisions, and in what form Whether minutes of the meeting be made and, if so, by whom and where they will be kept What will be done in the instances of disagreement between the DMC and the body to which they report	The DMC should report in writing to the TSC, usually within 3 weeks after the meeting. This should be copied to the trial statistician and may be sent via the trial office team. Unless the DMC is recommending that the trial protocol be change in some way, the letter to the TSC should not usually reveal any confidential information. An example of a letter from a DMC to the TSC recommending no action is presented in Appendix 2. Additionally, the letter should be copied to the PI, and Scientific officer appointed by the US Department of Defense, although their copies should have any confidential information (i.e. comments on data by group on the main outcome measures) removed and noted as such. Minutes from the meeting need not be detailed. A summary of the main points discussed with a list of clearly marked action points should be sufficient. It is recommended that separate minutes of open and closed session be made if the meeting is run in this format. The minutes for each session should be made only by someone who attends that session. This should be agreed at the start of the meeting. All members of the DMC should see and comment on the minutes. The DMC chair will be responsible for signing off all minutes. The TSC has ultimate responsibility for the trial and assumes primacy. However, the TSC should report to DMC how they have acted upon the DMC's recommendations. If the DMC has serious problems or concerns with the TSC decision, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. The meeting should be chaired by an external expert who is not directly involved with the trial. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting.

CONTENT	DETAIL
After the trial Publication of results The information about the DMC that will be included in published trial reports Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial Any constraints on DMC members divulging information about their deliberations after the trial has been published	The PI(s) have responsibility that trial results will be published in a correct and timely manner. The TSC is the committee that should oversee this process. At the end of the trial there may be a meeting to allow the DMC to discuss the final data with the principal trial investigator and give advice about data interpretation. DMC members will be named (unless they specifically ask not to be) in the primary published report. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper. DMC membership does not constitute authorship. The DMC members should be given at least 2 weeks, and if possible, a month, to read and comment on any draft publications that report outcome measures and/or details of the DMC. This may be done simultaneously to other groups reviewing the draft manuscript (e.g. TSC, trial investigators). The DMC should not discuss confidential issues from their involvement in the trial until 12 months after the primary trial results have been published, unless permission is agreed with the TSC. They should not trade in stock of companies affected by the trial until the results are public knowledge.

Figure 1: Trial design flow chart

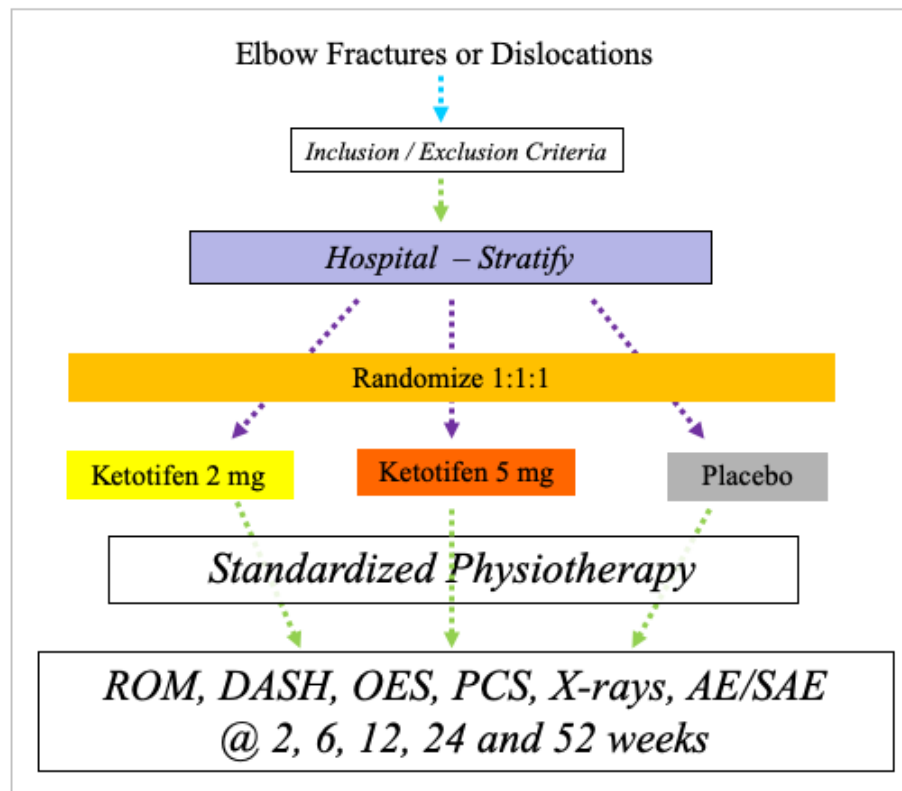
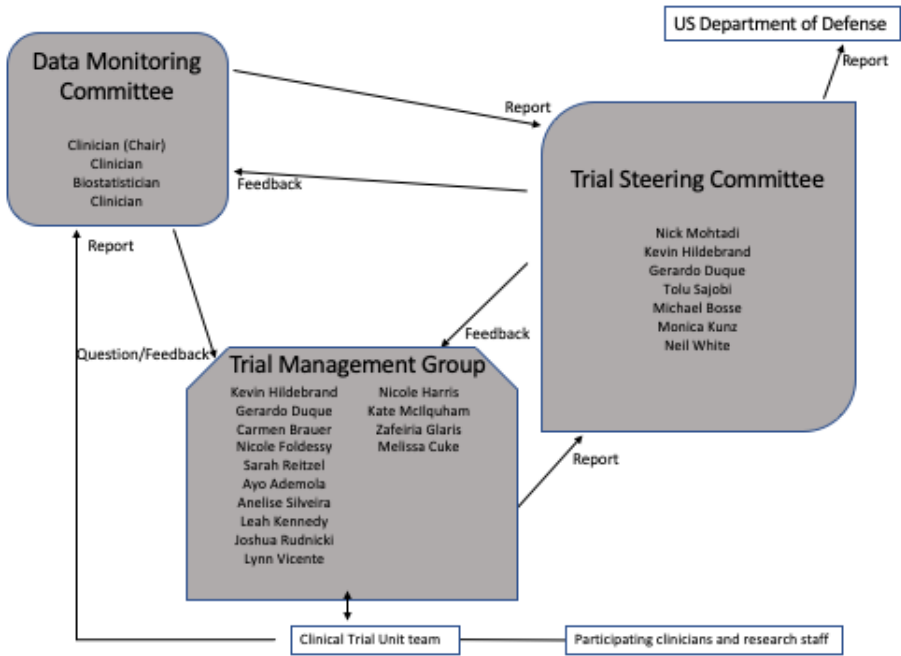


Figure 2: Relationships between trial committees



Abbreviations:

AE	Adverse Event
DASH	Disabilities Arm, Shoulder and Hand
DMC	Data Monitoring Committee
FDA	US Food and Drug Administration
HC	Health Canada
IND	Investigational New Drug
IRB	Institutional Review Board
mg	milligram
NOL	No Objection Letter
OES	Oxford Elbow Score
OHRP	Office for Human Research Protections
PCS	Pain Catastrophizing Scale
PI	Principal Investigator
ROM	Range of Motion
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
US	United States

Appendix 1: Conflicts of interest forms

Potential competing interests of Data Monitoring Committee members for *Prevention of posttraumatic contractures with Ketotifen 2 – PERK 2 / Kevin A. Hildebrand Principal Investigator*

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict eg strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication

Please complete the following section and return to the trials office.

☐
☐

No, I have no competing interests to declare

Yes, I have competing interests to declare (please detail below)

Please provide details of any
competing interests:

Name: _____

Signed: _____

Date: _____

Appendix 2: Details of the interim analysis plan

There is one formal interim analysis planned to assess the effect of Ketotifen Fumarate dosages compared with lactose placebo. The interim analysis will occur after 50% of the participants have been enrolled and followed for 3 months. The DSMB will evaluate whether there is an increased risk of Ketotifen Fumarate use compared with lactose placebo. The parameters determined *a priori* to discontinue the trial include any one of the following:

1. Greater than 2 times Fatal or Life-threatening SAEs that are Definitely or Probably related to Ketotifen Fumarate use (SUSAR).
2. Greater than 3 times difference in the DASH, PCS and OES between groups.
3. Greater than 3 times the number of participants with non-functional ROM (30 degrees to 130 degrees extension-flexion arc) between groups.

If any one of the above criteria are met, the DSMB will recommend to the TSC that the trial will be terminated prematurely.

PERK 2: Ketotifen to prevent contractures

PrEvention of posttraumatic contractuRes with Ketotifen 2
NCT03582176

Trial Management Group Charter

Version 2.0, February 10, 2020

(developed using MRC Clinical Trials Unit template TMG Charter version 3.01, 13-Mar-2006)

Authorised by:

Name: Kevin Hildebrand

Role: Chief Investigator

Signature: 

Date: 10-Feb-2020

Prepared by

Name: Kevin Hildebrand

Role: Chief Investigator

Signature: 

Date: 10-Feb-2020

CHARTER FOR TRIAL MANAGEMENT GROUP

CONTENT	DETAILS OF TMG
1. Introduction	
Name (& Sponsor's ID) of trial	Prevention of posttraumatic contractures with Ketotifen 2 – PERK 2 Sponsor – University of Calgary Principal Investigator – Kevin A. Hildebrand (NCT03582176)
Objectives of trial, including interventions being investigated	Primary Objective: To determine if Ketotifen given within 7 days of injury can reduce post-traumatic elbow joint contractures when compared to placebo. Secondary Objectives: 1) To ascertain the optimal dose of Ketotifen and 2) to compare adverse events in Ketotifen and placebo groups. (See Figure 1)
Outline of scope of Charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Trial Management Group (TMG) for this trial, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.
2. Roles and responsibilities	
A broad statement of the aims of the TMG	To manage the trial, including the clinical and practical aspects.
Specific roles of TMG members	- attend TMG meetings and advise on availability for future TMG meetings - input into and comment on the protocol and data collection instruments (DCI) - allow contact details to be included in the protocol - develop strategies to encourage recruitment and address any issues with recruitment at each trial centre - be involved in the day-to-day running of the trial by supporting the Chief Investigator (CI) and Clinical Trials Unit (CTU) - provide clinical or other expert guidance to CTU and participating sites on trial-based matters such as clinical and practical queries and interpretation of information recorded on DCIs - maintain confidentiality of any trial information that is not in the public domain - respond to trial correspondence and any questions in a timely fashion - input into the monitoring and classification of serious adverse events (SAEs) and reports from the Adverse Events Chair - input into the meetings of the Trial Steering Committee (TSC), if appropriate - input into the meetings of the Independent Data Monitoring Committee (IDMC), when appropriate (open sections only) - provide responses to any issues or concerns raised by TSC - consider the implications of any recommendations made by the IDMC and accepted by the TSC - be aware of accumulating external evidence and assess its impact and relevance - input into the development of the statistical analysis plan - input into the interpretation and writing up of the trial results - comment to TSC on external applications to use trial data Note that the CI has roles to perform in addition to those of being a member of the TMG. These are not detailed in this document.
3. Before or early in the trial	
Whether the TMG will have input into the protocol	The TMG will be responsible for finalising the protocol.
Any specific regulatory issues	A No Objection Letter (NOL) from Health Canada (Control number 218219) and Investigational New Drug (IND) approval from the US Food and Drug Administration (IND 136411) to use Ketotifen for prevention of Post-traumatic Joint Contractures.

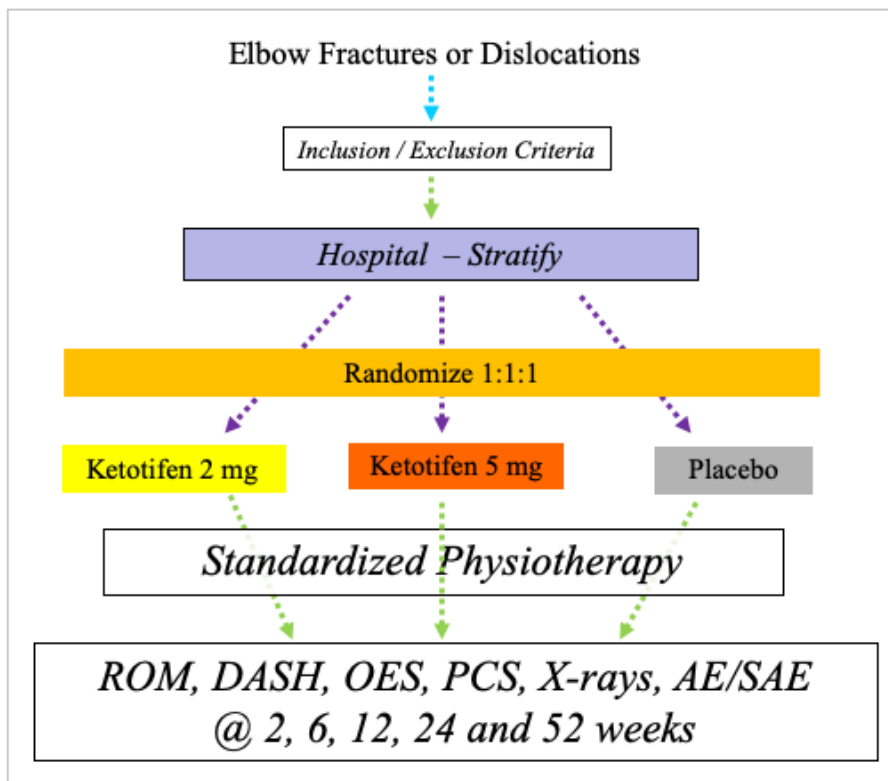
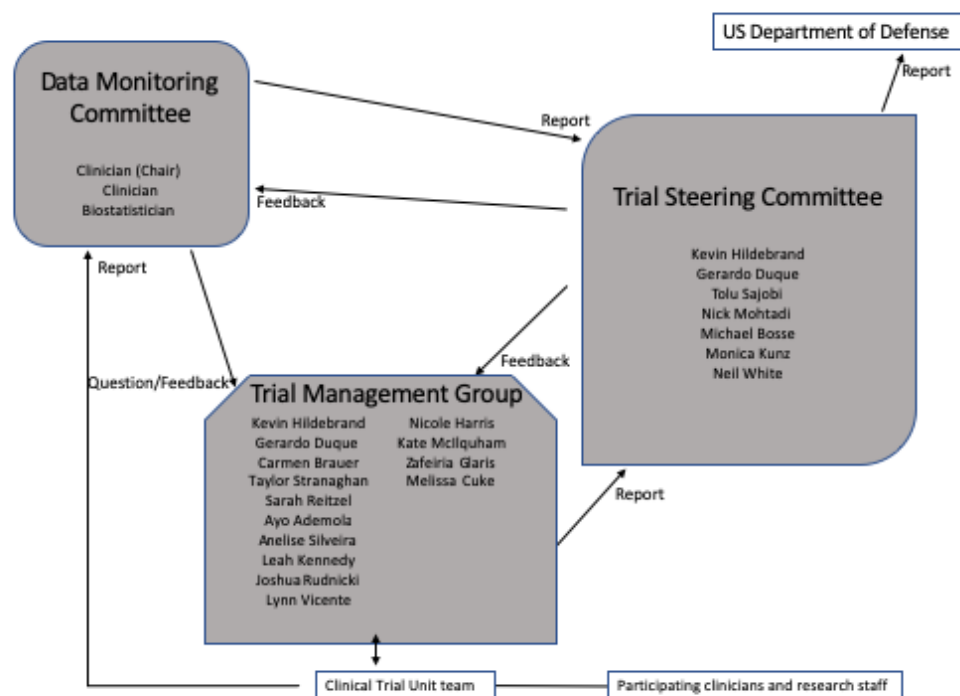
81 2

CONTENT	DETAILS OF TMG
	should be confirmed before accepting the invitation to join the TMG and CI/CTU must be informed immediately if this changes during the trial period. TMG members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. Organisation of meetings	
Expected frequency of TMG meetings Meeting setting When the TMG is quorate Can TMG members who cannot attend the meeting provide input What happens to members who do not attend meetings	Meeting frequency will be every 2 months. This will be shortened or lengthened as necessary related to trial needs and agreement with TMG members. Face-to-face meetings will normally be held, with teleconference options. Meetings will be organised by CTU staff. (See Section 8) The TMG report and agenda will be circulated before the meeting; TMG members who will not be able to attend the meeting may pass comments to the TMG Chair and CTU for consideration during the discussions. Members will be expected to send apologies in advance of any meeting they cannot attend. If a member neither attends nor sends apologies for a meeting, every effort will be made to ensure their availability for the next meeting. If a member does not attend nor send apologies for the following meeting, they will be asked if they wish to remain part of the TMG. If a member does not attend a third meeting in a row, they should be replaced, unless there are particular extenuating circumstances.
7. Trial reporting documentation	
Content of trial reports The people who will see accumulating trial data and interim analysis Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews) What will happen to the reports and papers	The TMG will be provided with reports of accrual, baseline characteristics, follow-up rates, data completion rates, and (serious) adverse events. The TMG members will not be privy to accumulating outcome measure data by trial arm – this will be reviewed by the IDMC only. The Adverse Events Chair, Carmen Brauer, will report to the TMG AE, SAE, Serious Adverse Reactions (SAR), Suspected Unexpected Serious Adverse Reactions (SUSAR) The accumulating trial data and interim analyses will be confidential. TMG members will not be privy to these interim reports; these will be viewed only by the IDMC. Accumulating data may be considered by the IDMC in the context of external evidence (e.g. from other trials/ systematic reviews). The TMG, notably the CI and/or the CTU team, should be responsible for identifying and collating the external information. TMG members would be expected to store securely copies of the reports to TMG, agendas and minutes, as well as copies of communications between meetings. All documentation should be considered confidential. The reports and papers should be disposed after the TMG is disbanded. The trials unit will keep a central record of all minutes, reports and correspondence by the TSC.
8. Decision making	
What decisions and recommendations will be open to the TMG	The TMG is responsible for the day-to-day running of the trial and can make decisions appropriate to this role. However, the TSC is the oversight body for the trial. TMG to TSC The TMG should refer to the TSC in some instances. The following are examples: • Request for additional interim analyses owing to concerns raised by external evidence • Stopping recruitment due to slow recruitment • Modifying target recruitment, or pre-analysis follow-up, based on any change to the assumptions underlying the original trial sample size calculation (but not on any emerging differences)

CONTENT	DETAILS OF TMG
How decisions will be reached within the TMG When the TMG is quorate	- Proposing substantial changes to the protocol, participant information sheet, eligibility criteria and other trial documentation - Request for endorsement for the early presentation of results - Request for endorsement for external data requests after the trial has closed TMG to IDMC The TMG can make recommendations to the IDMC. Possible recommendations from the TMG to the IDMC could include:- - Proposal of extra analyses for review by IDMC TMG alone Without referral to other committees, the TMG can:- - Propose strategies for dealing with poor recruitment rates, data quality according to consistency checks or site monitoring reports - Censure trial sites - Addition of new trial sites - Ordering medication for trial sites On all issues, every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; it is therefore best for the Chair to give their own opinion last. A total of 6 members that include: - Chair or Vice Chair - Trial Manager or Research Assistant - Trial Statistician or Data Manager
9. Reporting	
To whom will the TMG report their recommendations/concerns, and in what form Whether minutes of the meeting be made and, if so, by whom and where they will be kept What will be done if there is disagreement between the TMG and TSC	A standard report template will be used to provide information to the TSC. Additional information may be sent from the TMG to the TSC by writing via the TSC Facilitator. A short summary of each meeting with any action points clearly marked will be made. Initial drafts will be made by the CTU team before comments from the TMG members who were present. The TMG Chair will sign off these notes and a copy will be kept in a central file at the CTU. The TSC is the oversight body for the trial. If the TMG has serious problems or concerns with a TSC decision a meeting of these groups will be held. The information to be shown would depend upon the action proposed and the TSC's or TMG's concerns. Depending on the reason for the disagreement particularly sensitive trial data may have to be revealed to all or some of those attending such a meeting. The meeting would be Chaired by a senior member of the CTU staff, IDMC Chair or an external expert who is not directly involved with the trial. It is noted that the CI and member(s) of the CTU are represented on both the TMG and TSC.
10. After the trial	
Publication of results The information about the TMG that will be included in published trial reports Any constraints on TMG members divulging information about their trial experiences	At the end of the trial there will be meetings of the TMG to discuss the final data. The core of the Writing Committee will be drawn from the TMG. TMG members will promptly return comments on any circulated drafts. The IDMC and TSC members may be invited to give advice about data presentation and interpretation. Regardless of the authorship policy of the trial, TMG members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. TMG members should not divulge sensitive information about the ongoing trial unless specifically authorised by the TMG and, if appropriate, by the TSC, depending on the nature of the information. The TMG members may discuss issues from their involvement in the trial or trade in stock of a company making Ketotifen Fumarate 12 months after the primary trial results have been published, or when permission is agreed with the TSC.

Abbreviations and glossary

AE	Adverse event
CI	Chief Investigator
CMC	Carolinas Medical Center
CTU	Clinical Trials Unit
DCI	Data Collection Instruments
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
FMC	Foothills Medical Centre
MRC	Medical Research Council
MUHC	McGill University Health Centre
NOL	No Objection Letter
PLC	Peter Lougheed Centre
QHSC	Queen Elizabeth II Health Sciences Centre
RCH	Royal Columbian Hospital
SAE	Serious adverse event
SAR	Serious adverse reaction
SCH	Sturgeon Community Hospital
SHC	South Health Campus
SHSC	Sunnybrook Health Sciences Centre
SJH	St. Joseph's Hospital
SMH	St. Michael's Hospital
SPH	St. Paul's Hospital
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TOHC	The Ottawa Hospital Civic
TOHG	The Ottawa Hospital General
TSC	Trial Steering Committee
UMMC	University of Maryland Medical Center
UVMC	University of Vermont Medical Center

Figure 1: Diagram summarizing trial**Figure 2: Relationship of trial committees**

Annexe 1: Agreement and potential competing interests form

PERK 2 (NCT03582176): Agreement to join the Trial Management Group (TMG) and disclosure of potential competing interests

Please complete the following document and return to the Trial Manager.

(please initial box to agree)

☐	I have read and understood the TMG Charter version 2.0, February 10, 2020
☐	I agree to join the Trial Management Group for this trial
☐	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a TMG may be biased in some fashion is important for the credibility of the decisions made by the TMG and for the integrity of the trial.

Potential competing interests should be disclosed via the Clinical Trials Unit. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) TMG member should remove the conflict or stop participating in the TMG. **Table 1** lists potential competing interests.

☐	No , I have no potential competing interests to declare
☐	Yes , I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

Name: _____

Signed: _____

Date: _____

Table 1: Potential competing interests

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products

Note: This TMG charter was developed using MRC CTU template TMG Charter version 3.01, 13-Mar-2006

Annexe 2: Summary of changes from previous version

Version 1.0

This is version 1.0 of the TMG charter for this trial and is numbered this way for historical reasons. This is the first version.

Version 2.0

Changes to the committee member composition, update of abbreviations.

PERK 2: Ketotifen to prevent contractures

PrEvention of posttraumatic contractuRes with Ketotifen 2
NCT03582176

Trial Steering Committee Charter

Version 2.0, January 20, 2020

(developed using MRC Clinical Trials Unit template TSC Charter version 1.02, 13-Mar-2006)

Authorised by:

Name: Kevin Hildebrand

Role: Chief Investigator

Signature: 

Date: 20-Jan-2020

Prepared by

Name: Kevin Hildebrand

Role: Chief Investigator

Signature: 

Date: 20-Jan-2020

CONTENT		DETAILS OF TSC
1. Introduction		
Name (& Sponsor's ID) of trial		Prevention of posttraumatic contractures with Ketotifen 2 - PERK 2 Sponsor - University of Calgary Principal Investigator - Kevin A. Hildebrand Funder - United States Department of Defense (NCT03582176)
Objectives of trial, including interventions being investigated		Primary Objective: To determine if Ketotifen given within 7 days of injury can reduce post-traumatic elbow joint contractures when compared to placebo. Secondary Objectives: 1) To ascertain the optimal dose of Ketotifen and 2) to compare adverse events in Ketotifen and placebo groups. (See Figure 1)
Outline of scope of Charter		The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Trial Steering Committee (TSC) for this trial, including the timing of meetings, methods of providing information to and from the TSC, frequency and format of meetings and relationships with other trial committees.
Facilitation		A member of Clinical Trials Unit (CTU) staff (Gerardo Duque) will be nominated as a Facilitator for the trial. The Facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the TSC.
2. Roles and responsibilities		
A broad statement of the aims of the TSC		To act as the oversight body for this trial on behalf of the Sponsor/Funder.
Terms of reference		The role of the TSC is to provide oversight for the trial. It should also provide advice through its independent Chairman to the Trial Management Group (TMG), Department of Defense and CTU on all aspects of the trial.
Specific roles of TSC		- provide expert oversight of the trial - maintain confidentiality of all trial information that is not already in the public domain - make decisions as to the future continuation (or otherwise) of the trial - monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems - review regular reports of the trial from the CTU (sent on behalf of the Trial Management Group (TMG)) - receive letters of feedback from the independent data monitoring committee (IDMC) and consider their recommendations - assess the impact and relevance of any accumulating external evidence - monitor completion of data collection instruments (DCI) and comment on strategies from TMG to encourage satisfactory completion in the future - monitor follow-up rates and review strategies from TMG to deal with problems - censure sites that are deviating from the protocol - approve any proposals by the TMG concerning any change to the design of the trial, including additional substudies, changing inclusion/exclusion criteria, addition of sites - oversee the timely reporting of trial results - comment on the main trial manuscript - approve external or early internal requests for release of data or subsets of data
3. Before or early in the trial		
Whether the TSC will have input into the protocol		All potential independent TSC members should have opportunity to comment on the protocol as early as possible. Before recruitment begins the trial will have undergone review by the Sponsor/Funder (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential independent TSC member has major reservations about the trial (e.g. the protocol, the logistics, ethical concerns) they should report these to CTU and may decide not to accept the invitation to join. TSC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

CONTENT	DETAILS OF TSC
Whether the TSC will have input into the protocol	All potential independent TSC members should have sight of the protocol as early as possible. Before recruitment begins the trial will have undergone review by the Sponsor/Funder (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential independent TSC member has major reservations about the trial (e.g. the protocol, the logistics, ethical concerns) they should report these to CTU. TSC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Trial specific issues	
Any issues specific to the disease under study	Operative management of the elbow injuries is at the discretion of the participant in conjunction with the responsible site surgeon.
Any specific regulatory issues	The manufacturer of the active ingredient is not supporting the study beyond ensuring an adequate supply of medication. A No Objection Letter (NOL) from Health Canada (Control number 218219) and Investigational New Drug (IND) approval from the US Food and Drug Administration (IND 136411) to use Ketotifen for prevention of Post-traumatic Joint Contractures.
Any other issues specific to the treatment under study	Fracture healing is monitored by Xrays graded centrally by an MSK radiologist not involved with the active care of the participant and by the treating surgeon. Nonsteroidal anti-inflammatory drug use is documented during the study. The treatment group in the study is recorded. The radiologist is blind to all medications, and the surgeon and participant are blind to the randomized medication allocation.
Whether members of the TSC will have a contract	TSC members will not be asked to formally sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the TSC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Any observers (attendees who are not members) will sign a confidentiality agreement on the first occasion they attend a meeting (Annexe 2).
4. Composition	
Membership and size of the TSC	The majority of members of the TSC, including the Chair, should be independent of the trial (see section 5). Non-independent members will also be part of the TSC. The members of the TSC for this trial are: (1) Nicholas Mohtadi – Clinical Trialist (2) Mike Bosse – Site Principal Investigator, CMC (3) Tolulope Sajobi – Biostatistician (4) Kevin Hildebrand – Chief Investigator (5) Gerardo Duque – Clinical Trials Unit, Facilitator (6) Monica Kunz – Senior Clinical Research Coordinator, SHSC (7) Neil White - Site Principal Investigator, SHC
The Chair, how they are chosen and the Chair's role.	The Chair should have previous experience of serving on trial committees and experience of Chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area would be beneficial.
The responsibilities of the Facilitator	The Facilitator will be a member of staff at the CTU. The Facilitator will be responsible for arranging meetings of the TSC, coordinating reports, producing and circulating minutes and action points. The Facilitator will be the central point for all TSC communications between the TSC and other bodies, will be copied into all correspondence between TSC members and will be kept aware of trial issues as they arise.
The responsibilities of the clinical trial unit team	The trials unit team will produce a short report on the trial before each meeting of the TSC.
The responsibilities of the CI	The Chief Investigator (CI) is an important member of the TSC and no major decisions should be made without their involvement.
The responsibilities of the observers	Additional observers may be in attendance through (parts of) the TSC meetings in order to provide input on behalf of the trials unit, the trial's Sponsor/Funder or to provide specific relevant expertise.

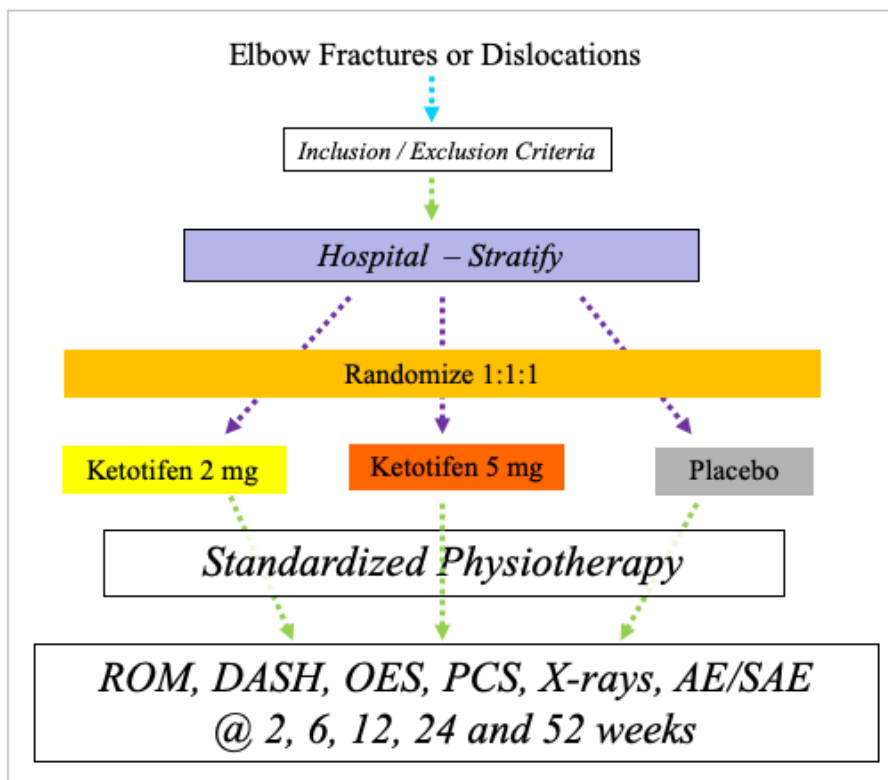
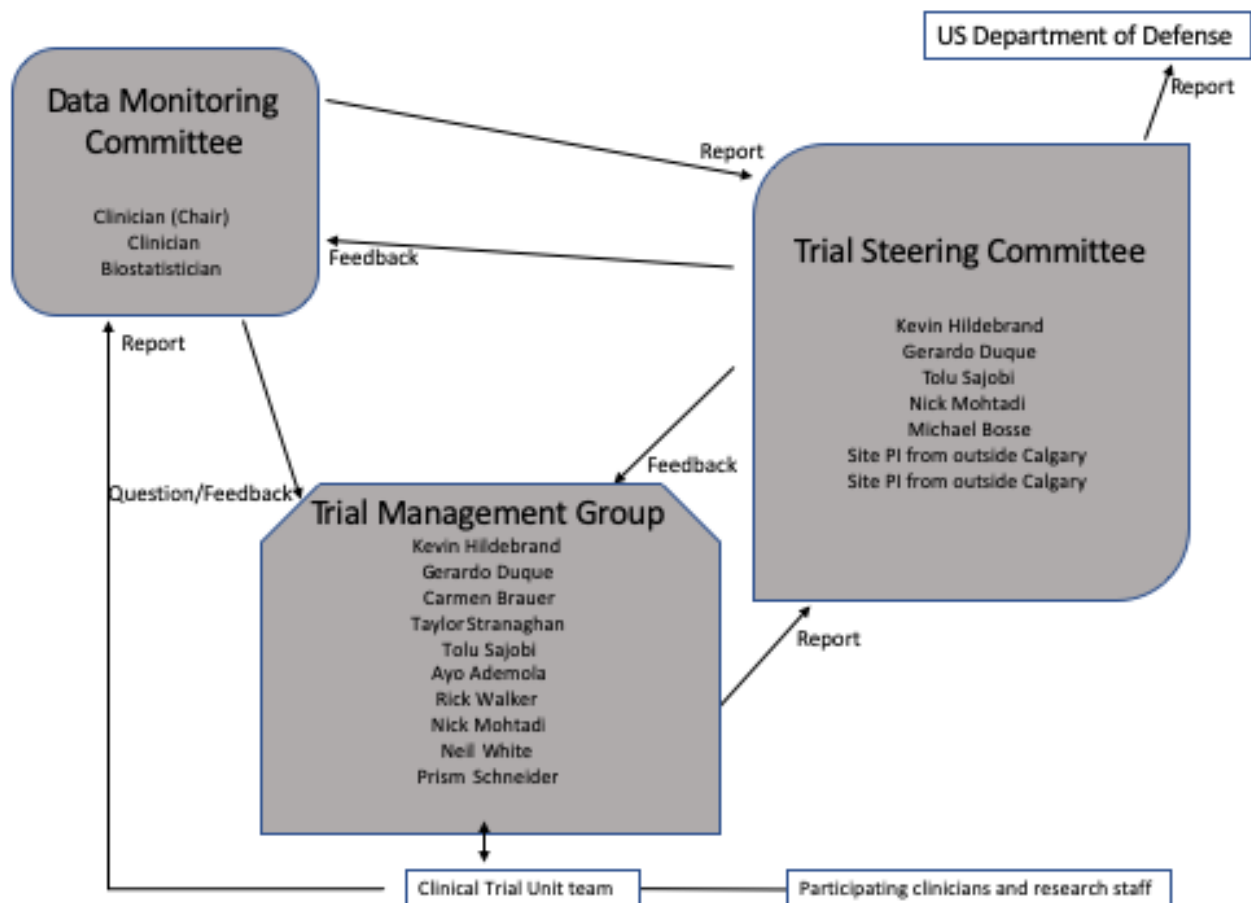
CONTENT	DETAILS OF TSC
5. Relationships	
Relationships with Chief Investigators, other trial committees (e.g. TMG and IDMC), Sponsor/Funder and regulatory bodies	The responsibilities of each trial committee are detailed in the protocol and in the respective Charters. The relationships between these groups are summarised in Figure 2.
Advisory and executive bodies	The TSC is the oversight body and is delegated the roles in Section 2 by the Sponsor. All substantial issues regarding the trial must go to the TSC for consideration. The IDMC is advisory to the TSC.
The need for TSC members to disclose information about any real or potential competing interests	Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1) TSC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting.
6. Organisation of meetings	
Expected frequency of TSC meetings	The TSC will meet at least twice yearly. At the request of the TSC, interim meetings will be organised. Many/major trial issues may need to be dealt with between meetings, by phone or by email. TSC members should be prepared for such instances.
Attendance of TSC members at meetings	Effort will be made for all members to attend. The CTU/Facilitator will work for a date that enables this to happen. It is accepted that the CI may not attend all meetings where major actions are not expected. Members who cannot attend in person should be encouraged to participate by teleconference. If, at short notice, any TSC members cannot attend then the TSC may still meet if at least one non Calgary member, two other members, and the Chair or vice Chair, will be present. If the TSC is considering a major action after such a meeting the TSC Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full TSC.
How TSC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Presence will be usually limited to the TSC members, observers from the Sponsor/Funder, CTU and the Facilitator. Other attendees may be invited for all or part of the meeting by the TSC. The observers are not members of the TSC but may be invited to provide expert input or to represent the funding bodies involved; other observers will be at the discretion of the TSC and the Facilitator but may include members of the TMG other than the CI.
Can TSC members who cannot attend the meeting input	If the report is circulated before the meeting, TSC members who will not be able to attend the meeting may pass comments to the TSC Chair, Facilitator or CTU contact for consideration during the discussions.
What happens to members who do not attend meetings	Members will be expected to send apologies in advance of any meeting they cannot attend. If a member neither attends nor sends apologies for a meeting, every effort will be made to ensure their availability for the next meeting. If a member does not attend nor send apologies for the following meeting, they will be asked if they wish to remain part of the TSC. If a member does not attend a third meeting in a row, they should be replaced, unless there are particular extenuating circumstances.
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be considered during meetings	A short report will be prepared by the CTU. This will report on accrual and any matters affecting the trial. Additionally, the material may include a report from the IDMC, requests from the TMG or draft publications. No trial outcome measure data will be presented by arm unless explicitly authorised by the IDMC (eg toxicity). Where relevant, accrual, compliance with follow-up and adherence to treatment may be presented by centre.

CONTENT	DETAILS OF TSC
Whether reports to the TSC be available before the meeting or only at/during the meeting The people who will see the accumulating data and interim analysis by randomised group Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews) To whom the TSC will communicate the decisions that are made What will happen to the papers after the meeting	It is usually helpful for the TSC to receive the report at least 1 week and preferably at least 2 weeks before any meetings. The accumulating trial data by arm and interim analyses will be confidential. These will be viewed only by the IDMC. The TSC will not be routinely privy to these interim reports. The IDMC will make recommendations to the TSC based on the interim data. Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the TSC members; it is a responsibility of the TMG. However, the TSC should continue to be made aware of other data that may impact on a trial. (See Section 9) TSC members would be expected to delete, destroy or store securely copies of the reports to and from the TSC, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential. The CTU/Facilitator will keep a central record of all minutes, reports and correspondence by the TSC.
8. Decision making	
What decisions will be open to the TSC The role of formal statistical methods How decisions or recommendations will be reached within the TSC When the TSC is quorate for decision-making Any specific issues relating to the trial design that might influence the proceedings	Based on recommendations from the IDMC, possible decisions include:- • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility or external evidence (this should generally involve a recommend from the IDMC to unblind the TSC to this data) • Modifying target recruitment, or pre-analysis follow-up, based on any change to the assumptions underlying the original trial sample size calculation (but not on any emerging differences) • Stopping one or more arms of a multi-arm trial • Sanctioning and/or proposing protocol changes Based on other factors, possible decisions include the decisions above and:- • Censuring centres for poor recruitment/poor data quality • Approving proposed protocol amendments or new trial sub-studies • Approving requests for early release of (subsets of) data • Approval of new centres or strategies to improve recruitment (altering inclusion/exclusion criteria) or follow-up Formal statistical methods may have been considered by the IDMC in making their recommendations to the TSC. These methods are usually used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. The IDMC will record reasons for disregarding a stopping guideline in the notes of their meetings and may choose to also note this in their report to the TSC if necessary. Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any decision is made. At least one non Calgary member, and the Chair or vice Chair, of the TSC should be present, plus a representative of the CTU and, if major action is to be considered, the CI. (See Section 3)

CONTENT	DETAILS OF TSC
9. Reporting	
To whom will the TSC report their recommendations/decisions, and in what form Whether minutes of the meeting be made and, if so, by whom and where they will be kept What will be done if there is disagreement between the TSC and other trial committees	The TSC will report their decisions (via the Facilitator) within 3 weeks of meeting to the TMG who will be responsible for implementing any actions resulting. The TSC may also provide feedback to the IDMC and, where appropriate, to the Sponsor/Funder. Copies of communications will pass through the CTU/Facilitator. Notes of key points and actions will be made by the CTU/Facilitator. This will include details of whether potential competing interests have changed for any attendees since the previous meeting. The draft minutes will be initially circulated for comment to those TSC members who were present at the meeting. The TSC Chair will sign off the final version of minutes or notes. The TSC is the oversight body for the trial. However, the TSC should have good reason before deciding not to accept requests from the TMG and recommendations from the IDMC. If there are serious problems or concerns with the TSC decision following an IDMC recommendation, a joint meeting of the TSC and IDMC should be held. The information to be shown would depend upon the action proposed and each committees' concerns. Depending on the reason for the disagreement confidential data and/or data by trial and may have to be revealed to all or some of those attending such a meeting; this would be minimised where possible. The meeting would be Chaired by a senior member of the CTU staff or an external expert who is not directly involved with the trial.
10. After the trial	
Publication of results The information about the TSC that will be included in published trial reports Any constraints on TSC members divulging information about their deliberations after the trial has been published	The TSC will oversee the timely analysis, writing up and publication of the main trial results. The members of the TSC will have the opportunity to read and comment on the proposed main publications of trial data prior to submission. This review may be concurrent to that of the trial investigators and IDMC. TSC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. TSC members may discuss issues from their involvement in the trial or trade in stock of a company making Ketotifen Fumarate 12 months after the primary trial results have been published, or when permission is agreed with the other trial committees and CTU. The TSC will decide when it is appropriate for the TMG and IDMC members to trade in stock.

Abbreviations and glossary

AE	Adverse Event
CI	Chief Investigator
CMC	Carolinas Medical Center
CTU	Clinical Trials Unit
DCI	Data Collection Instruments
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
MRC	Medical Research Council
NOL	No Objection Letter
PI	Principal Investigator
SAE	Serious Adverse Event
SHC	South Health Campus
SHSC	Sunnybrook Health Sciences Centre
TMG	Trial Management Group
TSC	Trial Steering Committee
US	United States

Figure 1: Diagram summarizing trial**Figure 2: Relationship of trial committees**

Annexe 1: Agreement and competing interests form for members

PERK 2 (NCT03582176): Agreement to join the Trial Steering Committee as a member and disclosure of potential competing interests

Please complete the following document and return to the Facilitator.

(please initial box to agree)

☐	I have read and understood the TSC Charter version 2.0, dated 20/Jan/2020
☐	I agree to join the Trial Steering Committee for this trial as a member
☐	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a TSC may be biased in some undisclosed fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Possible competing interests should be disclosed via the CTU. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) TSC member should remove the conflict or stop participating in the TSC. **Table 1** lists potential competing interests.

☐	No , I have no competing interests to declare other than involvement in the trial
☐	Yes , I have competing interests to declare (please detail below)

Please provide details of any competing interests:

Name: _____

Signed: _____

Date: _____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products

Note: This TSC charter was developed using MRC CTU template TSC Charter version 1.02, 13-Mar-2006

PERK 2 Trial Management Group Meeting #9

July 27th, 2020, 1:00pm-2:00pm MDT

Attendees: Ayoola Ademola, Taylor Stranaghan, Leah Schultz, Nicole Harris, Katie McIlquham, Stephanie Nathanail, Zafeiria Glaris, Jennifer Hidy and Gerardo Duque

Regrets: Dr. Kevin Hildebrand, Dr. Nicholas Mohtadi, Dr. Carmen Brauer, Josh Rudnicki, Sarah Reitzel, Michele Haugland, Lynn Vicente and Melissa Cuke

Meeting Start: 1:00pm MDT

1. Current state of COVID – 19 Response/Protocols Per Site

- a.** Peter Loughheed Centre has restarted PERK 2 activities, along with all other studies after receiving clearance from operational managers for all units/clinics. Currently PERK 2 is on hold to address REB requirements to add a “risk statement” on COVID-19 to the informed consent form
- b.** Foothills Hospital is on a unit-by-unit basis regarding research restart. A majority of the studies have been restarted at their site with a hold on PERK 2 as they also require the ICF modifications
- c.** Ottawa Hospitals (Civic and General) estimate a September restart date. Site coordinator stated they are having difficulties getting 4 x-ray views (missing oblique images). Coordinating Centre recommended going directly to the imaging department or emailing their staff prior to participants’ clinic visit to check on X-ray orders
- d.** St. Michael’s Hospital is experiencing a phased approach to restarting research. Clinical research will begin one study at a time based on risk assessments. They are currently in discussion with their local REB to determine if the estimated September restart date is likely to get back into the hospital/clinics, 1-2 studies at a time
- e.** St. Paul’s Hospital has begun recruitment restart. Unfortunately a COVID-19 outbreak has occurred within the NICU, nearby the OR where PERK 2 recruitment occurs. Research has been put back on hold currently. Recruitment restart is now estimated to be early-to-mid August

- f. Sturgeon Community Hospital recruitment restart may occur once updated ICF is submitted and approved. This hold is based on local REB approvals rather than AHS approvals. Coordinator has discussed a new University of Alberta institutional approval they may require by the Faculty of Medicine and Dentistry. They are currently looking into this as recruitment will be taking place off-site/campus

2. PERK 2 Remote Follow Ups

- a. No questions at this time regarding the procedures for remote follow-ups. Queries will continue to be generated every Friday by the Coordinating Centre and sent out in a report to all site coordinators. Payments will then be sent following the resolution of all queries.
- b. Remote images captured will be analyzed using the software “Image J”. Once data is captured through the software, measurements will be added to REDCap. A guidance document will be created by the Coordinating Centre once we are cleared to use the software as part of our protocol

3. COVID-19 Risk Assessment and ICF changes

- a. Based on updated COVID-19 exposure risk in hospitals, our local REB requires us to add information regarding the risks and how we are addressing them when participants attend follow-up visits or are approached for recruitment. Peter Lougheed Centre will provide sites with a template of this once we have it approved by local REB and regulatory agencies (Health Canada, FDA, and HRPO). Changes can be added to the original consent form, rather than as an addendum.

Meeting adjourned: 1:30 pm

Next TMG Meeting: Monday, August 31st, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT)

PERK 2 Trial Management Group Meeting #10

August 31st, 2020, 1:00pm-2:00pm MDT

Attendees: Gerardo Duque, Ayoola Ademola, Taylor Stranaghan, Josh Rudnicki, Leah Schultz, Sarah Reitzel, Katie McIlquam, Stephanie Nathanail, Zafeiria Glaris, and Melissa Cuke

Regrets: Dr. Kevin Hildebrand, Dr. Nicholas Mohtadi, Dr. Carmen Brauer, Nicole Harris, Milena Vincente, and Michele Haugland

Meeting Start: 1:00pm MDT

1. PERK 2 COVID-19 Protocol Waiver Update

- a. The updated waiver and new guidance document will be sent to all sites following acknowledgement from local REB at the Coordinating Center
- b. The guidance document will encompass a step-by-step process on gathering range of motion data, extracting from email, and uploading into Image J software for accurate ROM measurement

Question: Do we need to submit this waiver to our local REB/IRB if we are planning to continue to collect data in person?

Answer: Yes, all sites will need this updated in the case a lockdown were to happen again. It ensures all sites are able to collect data remotely in the future

2. Informed Consent Form & Drug Information Sheet changes

- a. Changes in the current consent are weight change information as well as the additional COVID-19 risk/measures from attending clinic visits in person
- b. Addressing “weight gain/loss” risks with potential participants during recruitment:
 - i. Weight gain is related to what is stated in the product monograph. Based on the indication for Ketotifen as a nasal spray for children with asthma, it is likely the weight gain is associated with a growing population. However, based on previous information gathered from the PERK 1 Trial, weight loss was observed in an adult population

3. PERK 2 Independent Monitoring Procedures

- a. **Coordinating Center and independent monitor are developing remote monitoring procedures.** This option will be provided to US based sites only. Further discussion and guidelines to be sent to sites once completed
- b. This visit occurs following the randomization of 3-5 participants at the site

4. COVID 19 Response & Restrictions per Active Sites

a. Site by site status update:

- i.** Peter Lougheed Centre (Taylor Stranaghan) is screening and recruiting with no limitations in clinics or OR. We have implemented the new consent and will be re-consenting all previously recruited participants
- ii.** Foothills Hospital (Leah Schultz) has no restrictions for on-site visits. Consent form and drug information sheets modifications have been approved. Awaiting approval from HRPO. No information for on-site monitor visits at this time. Monitor to contact by end of September
- iii.** South Health Hospital (Sarah Reitzel) has no restrictions on-site. They will be submitting modifications to REB the week of September 1st
- iv.** Maryland Hospital (Josh Rudnicki) not yet back in office but plan is to get back by week of September 7th. Staff turnover and training to occur next. Intending to begin recruitment in 2 weeks. Will submit modification soon
- v.** Sturgeon Hospital (Stephanie Nathanail) awaiting REB approval of ICF/DIS modifications. Once approved, Coordinating Center will submit forms to HRPO for approval. Site to reengage in person research thereafter
- vi.** Vermont (Melissa Cuke) research procedures are back in-person for screening and recruitment. Modification to be sent soon. Their hospital is not allowing in person monitoring for external visitors at this time. We are able to get remote monitoring accomplished for American sites – drafts to be reviewed by these sites by the end of next week
- vii.** St. Paul's Hospital (Zafeiria Glaris) just received approval to do on-site screening and recruitment. No on-site monitoring is allowed at this time. May see changes in the next month or so
- viii.** Ottawa Hospitals
 - 1.** Civic Campus (Nicole Harris) is screening/recruiting on a part time basis as staff is unable to be in office full time
 - 2.** Civic General Hospital (Katie McIlquham) awaiting approval from pharmacy to begin screening/recruiting processes. They will also be recruiting on a part-time basis. Both sites are unable to host on-site monitoring visits at this time

Meeting adjourned: 1:30 pm

Next TMG Meeting: Monday, September 28th, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT)

PERK 2 Trial Management Group Meeting #11

Sep 28, 2020, 1:00pm-2:00pm MDT

Attendees: Dr. Kevin Hildebrand, Ayoola Ademola, Gerardo Duque, Taylor Stranaghan, Leah Schultz, Sarah Reitzel, Stephanie Nathanail, Liane Jean, Nicole Harris, Katie McIlquam, and Zafeiria Glaris

Regrets: Dr. Nicholas Mohtadi, Dr. Carmen Brauer, Joshua Rudnicki and Melissa Cuke

Meeting start: 1:00pm MDT

1. PERK 2 COVID-19 Protocol Waiver Update

- a. The updated waiver and new guidance document will be sent to all sites following our approval at the coordinating center
- b. The guidance document will encompass a step-by-step process on safe picture extraction from email, use of Image J software for accurate ROM measurements, and research chart documentation procedures

2. REDCap Database: Query Resolution

- a. Coordinating Center will be generating ongoing queries on a weekly basis
- b. Query reports for October will be sent out on the first of the month
- c. Ideally, these queries should be completed prior to monitoring visit to ensure all questions are answered
- d. Reminder: research staff must collect the grade, expectancy, and relation to medication and report to the Sponsor of the AE/SAE within 72 hours of becoming aware of the event
 - i. SAE's are to be discussed with Sponsor team to determine reporting guidelines (i.e. possibly reporting to local site's REB)
 - ii. AE/SAE's entered into local AE logs are to be reviewed and signed by local PI for proper documentation

3. PERK 2 Independent Monitoring Procedures

- a. An Independent monitor is used to improve PERK 2 processes for the trial. It helps us to solve issues across all sites to facilitate better recruitment/follow up, data entry, query resolution, etc.
- b. American sites will be provided with a copy of our remote monitoring guidelines before their next visit (after randomization of 3-5 participants)
- c. Possible upcoming visits:
 - i. University of Vermont Medical Center
 - ii. The Ottawa Hospital - Civic and/or General)

- d. Four PERK 2 monitoring visits have been completed. We have identified ongoing trends from all sites which we will address in an official communication to sites soon. This is used to enhance site data collection across all sites.

4. COVID-19 Response & Restrictions per Active Sites

- a. Site by site status update:
 - i. Foothills Medical Hospital (Leah Schultz) is currently screening and recruiting for the PERK 2 trial. Foothills is addressing a COVID-19 outbreak and will expect to see new policies and procedures in the near future. A monitoring visit was completed on September 23, 2020
 - ii. South Health Hospital (Sarah Reitzel) has been approved to start screening/recruitment. Screening/recruitment restarted on September 28, 2020
 - iii. St. Michael's Hospital (Lynn Vincent) has slowly re-initiated trauma studies. Difficulty in PERK 2 restart as they have not yet recruited. Local team is awaiting response from their hospital to restart with PERK 2 screening and recruitment procedures
 - iv. Sturgeon Hospital (Stephanie) has received REB and AHS approval to be on site for screening and recruitment. Hopeful to start in-person visits to begin recruitment in the upcoming 1-2 weeks following modification approval by HRPO. Liane Jean has come on board as part of their research staff
 - v. St. Paul's Hospital (Zafeiria Glaris) restarted PERK 2 procedures last month. COVID-19 outbreak has been reported in a different unit which does not affect orthopedic trauma units.
 - vi. Ottawa Hospitals
 - 1. Civic Hospital (Nicole Harris) started screening and recruitment back in August. Staff are attending clinics/units only to see patients during screening and/or follow up visits.
 - 2. General Hospital (Katie McIlquham) started screening and recruiting 2 weeks ago. First post-COVID recruitment last week. More restrictive to go into the clinic therefore is able to go in 2 days/week. The screening will continue on a daily basis.

5. Questions

- a. Q: if a patient has been seen by an orthopaedic physician and determined to be an operative ORIF, what happens if they are randomized prior to surgery only to be treated as a total elbow replacement within surgery.
 - i. A: Under these circumstances, reviewing the inclusion/exclusion criteria with the attending physician prior to randomization is very important. When determining their eligibility during more severe cases, engage with the attending physician about the probability of addressing this as a total elbow rather than a standard ORIF procedure. If there is any uncertainty, it's best to approach the patient after surgery to potentially randomize into the trial.
 - 1. ***Note: hemiarthroplasty elbow replacements are eligible for the PERK 2 trial***

Meeting adjourned: 1:30 pm

Next TMG Meeting: Monday, October 26, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT)

PERK 2



PERK 2 Trial Steering Committee

Meeting #2

June 22nd, 2020, 5:30 – 7:00pm MDT

Attendees:

Dr. Kevin Hildebrand – Chief Investigator
Dr. Michael Bosse – Sponsor’s Medical Expert
Dr. Neil White – Site Principal Investigator, SHC
Dr. Tolulope Sajobi - BioStatistician
Monica Kunz, CCRP – Senior Clinical Research Coordinator, SHSC
Gerardo Duque, MA – Clinical Trials Unit, Facilitator

Regrets:

Dr. Nicholas Mohtadi – Chair/Clinical Trialist

1. COVID-19: Recruitment/Follow Up Restart Procedures

- a. Most inactive sites are unaware of when non-essential research activities can resume, including PERK 2 screening/recruitment/in-person follow ups
- b. Calgary sites (Peter Lougheed Centre, Foothills Medical Centre, and South Health Campus) need AHS clearance by operational managers of units/clinics to be used to restart. All sites are ready/close to ready to restart research activities
- c. St. Paul’s Hospital and University of Vermont are currently working on getting operational approvals to restart PERK 2 activities
- d. Comments:
 - i. South Health Campus and Peter Lougheed Centre
 1. Teams working on having only one person at the hospital. Interchanging days between coordinators, with some on call possibilities
 2. Recruitment focused on PERK 2 in units/clinics used before. No access to emergency room
 3. Ideally, recruitment would be from short stay or cast clinic, with surgeon possibly being first point of contact with participant about study
 4. Data collection to continue occurring remotely where needed. Measuring of ROM done by surgeon at clinic, if possible
- e. **COVID-19 Considerations:**
 - i. Second wave is probable. However, it is better to restart as soon as possible while there is time.

PERK 2



- ii. Closure may be more local rather than full study, depending on the state of COVID-19 status at each site
- iii. Carolina's Medical Center:
 - 1. Some studies will not be happening due to need of patient contact. They will be put into hibernation due to cost and limited amounts of no cost extensions
 - 2. Attempts at doing recruitment virtually (not in person) have met with dismal enrolment rates

f. What parts of PERK 2 activities have to be in person?

- i. Recruitment should be in person. For consenting procedures, provision of first ketotifen dose, and drug bottle
- ii. Study visits could be from home. Apart from ROM, most data can be gathered over the phone

2. COVID-19: Remote data collection

- a. Remote data collection has been going well overall
- b. ROM image is the one that presents the biggest limitation, but coordinators have been able to establish good contact with participants to improve the process
- c. Coordinators have been encouraged to engage surgeons providing in person follow ups to get ROM measurements
- d. For questionnaires, coordinators are able to email a link to REDcap surveys. Answers go directly into the database

3. Health Canada – Review of Protocol V5.0

- a. Health Canada advisor accepted Protocol V5.0 changes January 9, 2020 as a notification
- b. However, re-review of Protocol V5.0 as an amendment was requested May 22nd, 2020
- c. Health Canada asked for weight gain to be added as a side effect to the informed consent
- d. Coordinating center waiting on new No Objection letter to be sent to all sites, and the new ICF to be submitted for REB approval at all sites
- e. Already active sites would resume recruitment with previous ICF, which shows weight gain as a side effect

PERK 2



4. Data Monitoring Committee

- a. Invites to the DMC were sent in the last month
- b. The following individuals have accepted their invite:
 - i. Dr. Helen Razmjou (Advanced Practice Physiotherapist – Clinical Trialist)
 - ii. Dr. Kim Madden (Biostatistician)
 - iii. Dr. Sam Morshed (Orthopedic Surgeon)
- c. Invitations awaiting a response:
 - i. Dr. James Wright (Pediatric Orthopedic Surgeon)
 - 1. TSC will give him one more week to respond to invite
 - 2. The 2nd Invite was resent to his current OMA address
- d. **Considerations:**
 - i. Indemnity clause available to DMC members?
 - 1. Coordinating center engaging legal to confirm if this available to invitees
 - 2. Current thought is that each individual institution provides this coverage to DMC members and it is for site operational support staff for the trial, but Dr. Madden's institution does not provide this coverage to DMC members, as they act as independent scientists

5. Site restart considerations

- a. Canadian sites to wait on Health Canada's No Objection Letter to recent amendment
 - i. Canadian sites active before COVID-19 could restart using previous consent which already contains weight gain as a side effect
 - ii. After receiving no objection letter, they would submit the new ICF for future use
 - iii. Sites to confirm if they have operational approval from their units/clinics
- b. American sites can restart with approved documents once they have operational approval at their site, as they are not subject to Health Canada restrictions
- c. Coordinating site will put together an official memo covering all details of PERK 2 restart

Next TMG meeting: Monday, September 21st, 2020 at 5:30pm – 7:00pm MDT



PERK 2 Trial Steering Committee
Meeting #3
September 21st, 2020, 5:30 – 7:00pm MDT

Attendees:

Dr. Kevin Hildebrand – Chief Investigator
Dr. Michael Bosse – Sponsor’s Medical Expert
Dr. Neil White – Site Principal Investigator, SHC
Monica Kunz, CCRP – Senior Clinical Research Coordinator, SHSC
Gerardo Duque, MA – Clinical Trials Unit, Facilitator

Regrets:

Dr. Nicholas Mohtadi – Chair/Clinical Trialist
Dr. Tolulope Sajobi - BioStatistician

1. COVID-19: Recruitment/Follow Up Restart Procedures

- a. Six PERK 2 trial sites are actively screening/recruiting. 4 new participants have been recruited since sites reopened in mid-August.
 - i. Peter Lougheed Centre
 - ii. Foothills Medical Hospital
 - iii. The Ottawa Hospital – Civic Campus
 - iv. The Ottawa Hospital – General Campus
 - v. St. Paul’s Hospital
 - vi. University of Vermont Medical Center
- b. Current limitations/delays for site restart include:
 - i. Local REB reviewing ICF and Drug Information Sheet modifications requested by Health Canada
 - ii. Consequent review of modifications by the DoD’s HRPO office for final implementation
 - iii. Addition of COVID-19 risks and measures to informed consent at certain sites (Calgary based sites, and Sturgeon Community Hospital in Edmonton)
 - iv. Local operational restrictions keeping interventional studies from restarting due to COVID-19 restrictions



2. COVID-19: Remote data collection and ROM picture analysis

- a. Protocol waiver has been updated to include ROM picture analysis procedures using ImageJ
- b. Updated guidance document is under review by the coordinating centre's REB
- c. Once approved, documents will be disseminated to all sites for local implementation

i. Questions

1. Dr. Neil White: *Can remote data/ROM collection be done even if pt. is not seen due to COVID-19 restrictions?*

- a. Yes. Protocol waiver covers participant's decision to not attend clinic.

2. Monica Kunz, CCRP: *Does the guidance address pt. confidentiality in its processes?*

- a. Yes. Step by step instructions are given to maintain the participant's confidentiality throughout the analysis.

3. Protocol v6.0 – Possible modifications

- a. Two additions to the protocol have been proposed:
 - i. Adding the protocol waiver and guidance documents as a "Pandemic Plan" appendix to the protocol. Ideally, this would address the trials needs in case we experience another lockdown.
 - ii. Adding a "partial withdrawal" option acknowledging the possibility of continuing to follow a participant through chart reviews and a one year call if they do not want to actively complete certain aspects of the trial

4. Adverse Event and Serious Adverse Event – Report Review

- a. 32 adverse events have been reported by 22 study participants. In regards to adverse event grading, we have observed 29 mild, 3 moderate, and 0 severe adverse events.
- b. 1 serious adverse event (wound dehiscence) has been reported by 1 participant. This serious adverse event was graded as severe, expected and unrelated to use of trial medication.
- c. Coordinating center has established the following process to review AE's and SAE's occurring in the trial
 - i. Site informs Dr. Hildebrand and Gerry (under Sponsor role) within 72 hours of AE/SAE being reported.
 - ii. Discussion is done with site to determine grade, expectancy, and relatedness to trial medication.
 - iii. If questions arise from the review, it is brought to Dr. Carmen Brauer (PERK 2 trial safety research monitor) for final review and decision on



having to report the AE/SAE or not before the respective 7 or 15 day regulatory reporting deadlines.

- iv. For consistent control, Gerry meets with Dr. Brauer every two weeks to discuss latest AE's reported and how to ensure proper documentation.

5. Data Monitoring Committee:

- a. Four individuals have accepted our invitation to become part of the DMC:
 - i. Dr. Helen Razmjou (Advanced Practice Physiotherapist – Clinical Trialist)
 - ii. Dr. Kim Madden (Biostatistician)
 - iii. Dr. Sam Morshed (Orthopedic Surgeon)
 - iv. Dr. James Wright (Pediatric Orthopedic Surgeon)
- b. We've confirmed with our trial insurance representative that the committee is covered as our "Scientific Advisory Board"
- c. As reflected in the DMC charter, first meeting is to be completed after a year of starting recruitment (limited due to COVID-19) or reaching 70 participants (10% of sample) enrolled.
- d. Expectations of the first DMC meeting include:
 - i. Confirming the nominated chair
 - 1. TSC chair to confirm who will be nominated as chair
 - 2. DMC to later confirm the nomination during first meeting
 - ii. Discuss inner workings of the DMC
 - iii. Creating first report for TSC
 - 1. Data to build report is to be blinded to the treatment, but un-blinded to the group. Option to un-blind (only the DMC) to be made if a safety concern comes up
 - 2. The DMC chair would ask what data they require to make the appropriate determinations during the meeting

6. Action items:

- a. Follow up with DMC invitees to complete the "Competing Interests" form in the DMC charter
- b. Dr. Kevin Hildebrand to engage Dr. Nicholas Mohtadi and Dr. Tolulope Sajobi to confirm who could be nominated as DMC chair
 - i. Engage members to confirm who is able to take on the position
 - ii. Possibly confirming the position and engaging the committee sooner rather than later

Next TMG meeting: Monday, December 14th, 2020 at 5:30pm – 7:00pm MDT

Gerardo Duque

From: Madden, Kim
Sent: Tuesday, June 09, 2020 3:07 PM
To: Nicholas Mohtadi
Cc: Gerardo Duque; Kevin A. Hildebrand
Subject: RE: Data Monitoring Committee PERK2

[△EXTERNAL]

Hi Dr. Mohtadi,

I am happy to accept the invitation to be a part of the DMC for this trial. I would just like to request clarification regarding indemnification for DMC members. Typically, home institutions (McMaster in my case) do not provide legal protection for DMC members who face legal action, since we are acting as independent scientists. Does your institution provide legal protection for DMC members? Or will there be an indemnification agreement? I'm sure we won't get sued, but it's great to be prepared for all circumstances.

Thanks,
Kim

Kim Madden, PhD
Assistant Professor (PT) | McMaster University
Research Manager | St. Joseph's Healthcare Hamilton
Department of Surgery
Department of Health Research Methods, Evidence & Impact
G841-50 Charlton Ave E
Hamilton ON L8N 4A6

From: Nicholas Mohtadi
Sent: June 4, 2020 8:39 AM
To: Madden, Kim
Cc: Gerardo Duque ; Kevin A. Hildebrand
Subject: Data Monitoring Committee PERK2

Dear Dr. Madden,

It is my privilege to invite you to serve on the Data Monitoring Committee (DMC) for the Phase III multicentre clinical trial, “**Pr**Evention of posttraumatic joint contractu**Res** using **Ketotifen 2 – PERK 2**”. The principal investigator is Dr. Kevin Hildebrand. Funding has been provided by the US Department of Defense – Congressionally Directed Medical Research Programs. Your name was suggested by our Trial Steering Committee (TSC). This trial looks to determine if Ketotifen Fumarate given within 7 days of surgically treated elbow fractures and dislocations can reduce post-traumatic elbow joint contractures when compared to placebo.

In considering this committees' member responsibilities, we have appended information for your review. Included you will find the following documents: A brief summary of the DMC roles and responsibilities, a summary protocol of the trial and the DMC Charter document which provides the details of involvement. As a DMC member, you would have the following responsibilities:

- Safeguard the interests of the trial's participants, potential participants, investigators and sponsor
- Assess the safety and efficacy of the trial's interventions
- Monitor the trial's overall conduct, and protect its validity and credibility

As you can likely appreciate the trial is currently on hold because of the COVID-19 pandemic. We need to spend this time finalizing the remaining logistical details. Our success in this clinical trial is dependent on the commitment of its committee members and the work done together with all involved.

Please let me know your decision as soon as possible, but hopefully no later than June 15th.

We hope you accept our invitation and look forward to working with you in making the PERK 2 trial a success. If you have any questions, do not hesitate to contact our team (Gerry Duque our trial manager Dr. Kevin Hildebrand or me

Respectfully,

Nick Mohtadi MD MSc FRCSC; Dip Sport Med (CASEM)
Chair Trial Steering Committee PERK-2

Clinical Professor Dept. Surgery Cumming School of Medicine
Adjunct Professor Faculty of Kinesiology
Medical Director University of Calgary Sport Medicine Centre

Gerardo Duque

From: Morshed, Saam
Sent: Thursday, June 18, 2020 8:40 AM
To: Nicholas Mohtadi
Cc: Gerardo Duque; Kevin A. Hildebrand
Subject: Re: Data Monitoring Committee PERK2

[△EXTERNAL]

Dear Nick and Kevin, I am happy participate. Please provide more information as we get closer to trial initiation.

Best regards,

Saam Morshed

On Jun 18, 2020, at 4:58 AM, Nicholas Mohtadi

Dear Dr. Morshed,

I am sending a gentle reminder regarding our request to have you provide your expertise and help in our trial.

It is my privilege to invite you to serve on the Data Monitoring Committee (DMC) for the Phase III multicentre clinical trial, “**PrE**vention of posttraumatic joint contractu**Res** using **Ketotifen 2 – PERK 2**”. The principal investigator is Dr. Kevin Hildebrand. Funding has been provided by the US Department of Defense – Congressionally Directed Medical Research Programs. Your name was suggested by our Trial Steering Committee (TSC). This trial looks to determine if Ketotifen Fumarate given within 7 days of surgically treated elbow fractures and dislocations can reduce post-traumatic elbow joint contractures when compared to placebo.

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As a DMC member, you would have the following responsibilities:

- Safeguard the interests of the trial’s participants, potential participants, investigators and sponsor
- Assess the safety and efficacy of the trial’s interventions
- Monitor the trial’s overall conduct, and protect its validity and credibility

As you can likely appreciate the trial is currently on hold because of the COVID-19 pandemic. We need to spend this time finalizing the remaining logistical details. Our success in this clinical trial is dependent on the commitment of its committee members and the work done together with all involved.

Please let me know your decision as soon as possible, but hopefully no later than June 30th.

We hope you accept our invitation and look forward to working with you in making the PERK 2 trial a success. If you have any questions, do not hesitate to contact our team (Gerry Duque our trial manager Dr. Kevin Hildebrand or me at

Respectfully,

Nick Mohtadi MD MSc FRCSC; Dip Sport Med (CASEM)
Chair Trial Steering Committee PERK-2

Clinical Professor Dept. Surgery Cumming School of Medicine
Adjunct Professor Faculty of Kinesiology
Medical Director University of Calgary Sport Medicine Centre

<NM final PERK2_Protocol_SummaryStatement_Draft2_20200511 (002).docx>

<NM PERK2_DMC_Responsibilities_ShortNote (002).docx>

<NM FinalPERK 2 - DMC charter version 2.0 Draft 2 20200526.docx>

<Morshed letter DMC committee invite.docx>

Gerardo Duque

From: Razmjou, Helen
Sent: Friday, June 05, 2020 2:30 PM
To: Nicholas Mohtadi
Cc: Kevin A. Hildebrand; Gerardo Duque
Subject: RE: Data Monitoring Committee for PERK 2 Trial

[△EXTERNAL]

Good Day Nick,

Hope all is well,

Thank you for your invitation, sounds like an interesting study. I will be happy to assist.

I assume that I have to send you a formal letter, indicating my agreement.

Best regards,

Helen

*Helen Razmjou, MSc., PT, PhD
Associate Scientist, Sunnybrook Research Institute
Assistant Professor, Department of Physical Therapy, University of Toronto
Advanced Practice Physical Therapist, Bone and Joint Program
Holland Orthopaedic & Arthritics Centre
Sunnybrook Health Sciences Centre*

From: Nicholas Mohtadi **Sent:** Thursday, June 04, 2020 8:32 AM
To: Razmjou, Helen
Cc: Kevin A. Hildebrand; Gerardo Duque
Subject: Data Monitoring Committee for PERK 2 Trial

CAUTION: External mail. Do not click on links or open attachments you do not trust.

Dear Dr. Razmjou,

It is my privilege to invite you to serve on the Data Monitoring Committee (DMC) for the Phase III multicentre clinical trial, “PrEvention of posttraumatic joint contractuRes using Ketotifen 2 – PERK 2”. The principal investigator is Dr. Kevin Hildebrand. Funding has been provided by the US Department of Defense – Congressionally Directed Medical Research Programs. Your name was suggested by our Trial Steering

Committee (TSC). This trial looks to determine if Ketotifen Fumarate given within 7 days of surgically treated elbow fractures and dislocations can reduce post-traumatic elbow joint contractures when compared to placebo.

In considering this committee's member responsibilities, we have appended information for your review. Included you will find the following documents: A brief summary of the DMC roles and responsibilities, a summary protocol of the trial and the DMC Charter document which provides the details of involvement. As a DMC member, you would have the following responsibilities:

- Safeguard the interests of the trial's participants, potential participants, investigators and sponsor
- Assess the safety and efficacy of the trial's interventions
- Monitor the trial's overall conduct, and protect its validity and credibility

As you can likely appreciate the trial is currently on hold because of the COVID-19 pandemic. We need to spend this time finalizing the remaining logistical details. Our success in this clinical trial is dependent on the commitment of its committee members and the work done together with all involved.

Please let me know your decision as soon as possible, but hopefully no later than June 15th.

We hope you accept our invitation and look forward to working with you in making the PERK 2 trial a success. If you have any questions, do not hesitate to contact our team (Gerry Duque our trial manager Gerardo.duque@ucalgary.ca Dr. Kevin Hildebrand hildebrk@ucalgary.ca or me at mohtadi@ucalgary.ca

Respectfully,

Nick Mohtadi MD MSc FRCSC; Dip Sport Med (CASEM)
Chair Trial Steering Committee PERK-2

Clinical Professor Dept. Surgery Cumming School of Medicine
Adjunct Professor Faculty of Kinesiology
Medical Director University of Calgary Sport Medicine Centre

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Gerardo Duque

From: Wright, Jim
Sent: Tuesday, June 30, 2020 5:13 AM
To: Nicholas Mohtadi
Cc: Gerardo Duque; Kevin A. Hildebrand
Subject: Re: [EXTERNAL]: FW: Data Monitoring Committee

[△EXTERNAL]

Hi Nick
Happy to help
Jim

JAMES WRIGHT CM MD MPH FRCSC FRCS (Ed)
Chief, Economics, Policy & Research

Ontario Medical Association
[150 Bloor St. West, Suite 900, Toronto, Ontario M5S 3C1](#)

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On 18 Jun 2020, at 07:45, Nicholas Mohtadi wrote:

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Dear Dr Wright,

It is my privilege to invite you to serve on the Data Monitoring Committee (DMC) for the Phase III multicentre clinical trial, “**PrE**vention of posttraumatic joint contractu**Res** using **Ketotifen 2 – PERK 2**”. The principal investigator is Dr. Kevin Hildebrand. Funding has been provided by the US Department of Defense – Congressionally Directed Medical Research Programs. Your name was suggested by our Trial Steering Committee (TSC). This trial looks to determine if Ketotifen Fumarate given within 7 days of surgically treated elbow fractures and dislocations can reduce post-traumatic elbow joint contractures when compared to placebo.

In considering this committees’ member responsibilities, we have appended information for your review. Included you will find the following documents: A brief summary of the DMC roles and

responsibilities, a summary protocol of the trial and the DMC Charter document which provides the details of involvement.

As a DMC member, you would have the following responsibilities:

- Safeguard the interests of the trial's participants, potential participants, investigators and sponsor
- Assess the safety and efficacy of the trial's interventions
- Monitor the trial's overall conduct, and protect its validity and credibility

As you can likely appreciate the trial is currently on hold because of the COVID-19 pandemic. We need to spend this time finalizing the remaining logistical details. Our success in this clinical trial is dependent on the commitment of its committee members and the work done together with all involved.

Please let me know your decision as soon as possible, but hopefully no later than June 30th.

We hope you accept our invitation and look forward to working with you in making the PERK 2 trial a success. If you have any questions, do not hesitate to contact our team (Gerry Duque our trial manager Dr. Kevin Hildebrand or me at

Respectfully,

Nick Mohtadi MD MSc FRCSC; Dip Sport Med (CASEM)
Chair Trial Steering Committee PERK-2

Clinical Professor Dept. Surgery Cumming School of Medicine
Adjunct Professor Faculty of Kinesiology
Medical Director University of Calgary Sport Medicine Centre

<NM final PERK2_Protocol_SummaryStatement_Draft2_20200511 (002).docx>
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<Wright letter DMC committee invite.docx>

STUDY PROTOCOL

Open Access



Prevention of posttraumatic contractures with Ketotifen 2 (PERK 2) – protocol for a multicenter randomized clinical trial

Ayoola Ademola^{1,2*} , Kevin A. Hildebrand^{1,3}, Prism S. Schneider^{1,2,3}, Nicholas G. H. Mohtadi^{1,3}, Neil J. White³, Michael J. Bosse⁴, Alexandra Garven³, Richard E. A. Walker^{1,5} and Tolulope T. Sajobi²

Abstract

Background: Injuries and resulting stiffness around joints, especially the elbow, have huge psychological effects by reducing quality of life through interference with normal daily activities such as feeding, dressing, grooming, and reaching for objects. Over the last several years and through numerous research results, the myofibroblast-mast cell-neuropeptide axis of fibrosis had been implicated in post-traumatic joint contractures. Pre-clinical models and a pilot randomized clinical trial (RCT) demonstrated the feasibility and safety of using Ketotifen Fumarate (KF), a mast cell stabilizer to prevent elbow joint contractures. This study aims to evaluate the efficacy of KF in reducing joint contracture severity in adult participants with operatively treated elbow fractures and/or dislocations.

Methods/design: A Phase III randomized, controlled, double-blinded multicentre trial with 3 parallel groups (KF 2 mg or 5 mg or lactose placebo twice daily orally for 6 weeks). The study population consist of adults who are at least 18 years old and within 7 days of injury. The types of injuries are distal humerus (AO/OTA type 13) and/or proximal ulna and/or proximal radius fractures (AO/OTA type 2 U1 and/or 2R1) and/or elbow dislocations (open fractures with or without nerve injury may be included). A stratified randomization scheme by hospital site will be used to assign eligible participants to the groups in a 1:1:1 ratio. The primary outcome is change in elbow flexion-extension range of motion (ROM) arc from baseline to 12 weeks post-randomization. The secondary outcomes are changes in ROM from baseline to 6, 24 & 52 weeks, PROMs at 2, 6, 12, 24 & 52 weeks and impact of KF on safety including serious adverse events and fracture healing. Descriptive analysis for all outcomes will be reported and ANCOVA be used to evaluate the efficacy KF over lactose placebo with respect to the improvement in ROM.

Discussion: The results of this study will provide evidence for the use of KF in reducing post-traumatic joint contractures and improving quality of life after joint injuries.

Trial registration: This study was prospectively registered (July 10, 2018) with ClinicalTrials.gov reference: [NCT03582176](https://clinicaltrials.gov/ct2/show/study/NCT03582176).

Keywords: RCT, Ketotifen Fumarate, Contractures, DASH, OES, PCS, ROM

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Full list of author information is available at the end of the article



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Background

Joint contractures develop as a consequence of trauma, arthritis, or reconstructive procedures and can be functionally debilitating [1]. These injuries occur most commonly in the working age group (20–60 years), thus, representing a significant societal burden in North America [2–5]. Analysis of the Calgary Health Region database revealed that approximately 1200 elbow fractures or dislocations occurred in 2002–2005 [2–5]. These rates extrapolated to the Canadian population resulted in an estimated 20,000 elbow fractures or dislocations per year nationally. Assuming 1 in 8 will develop a joint contracture requiring operative intervention, an estimated > 2500 operative procedures per year for elbow contracture in Canada [6–10]. Extrapolated to the US, this would yield over 25,000 operative procedures annually.

Over the last 20 years, our laboratory research has implicated a myofibroblast-mast cell-neuropeptide axis of fibrosis in post-traumatic joint contractures [11]. Ketotifen Fumarate (KF) is a medication that has anti-anaphylactic properties, due to the prevention of the synthesis and/or release of growth factors and mediators from mast cells. It has been used in the treatment of chronic asthma for over 40 years in humans. Post-market surveillance has confirmed the safety of KF (11, Bassler). Through a preclinical rabbit model of post-traumatic joint contractures, we have shown that KF, decreased contracture severity concomitant with decreased numbers of myofibroblasts, mast cells, neuropeptide containing nerve fibres, and measures of fibrosis in the joint capsule in a dose-dependent fashion [12–14]. It is the first and only agent demonstrating both a significant decrease in contracture severity in preclinical trials and a wide safety profile. A previously conducted pilot randomized clinical trial (NCT01902017) demonstrated safety of KF and coupled with preclinical animal studies informed the need to increase the sample size, use multiple doses to examine for a dose response, and further refine the trial population to more severe injuries requiring an operation in the Phase III randomized clinical trial (RCT).

The primary objective is to evaluate the efficacy of KF in reducing post-traumatic elbow joint contractures when compared to placebo in participants with elbow fractures or dislocations administered within 7 days of injury and for a duration of 6 weeks. There are two secondary objectives i.e. (1) Evaluate the efficacy of KF over lactose placebo with respect to Disability Arm Shoulder Hand (DASH), Oxford Elbow Score (OES), and Pain Catastrophizing Scale (PCS), (2) Evaluate the impact of KF on safety including serious adverse events, fracture healing and re-operation rates.

This is a Phase III randomized, controlled blinded multi-centre efficacy trial with three parallel groups and a primary endpoint of elbow flexion-extension range of motion (ROM) arc at 12 weeks post-randomization (Fig. 1). Eligible participants will be randomized to receive KF 2 mg, KF 5

mg, or lactose placebo (PL) in a 1:1:1 allocation ratio. The medication is administered orally twice daily for 6 weeks.

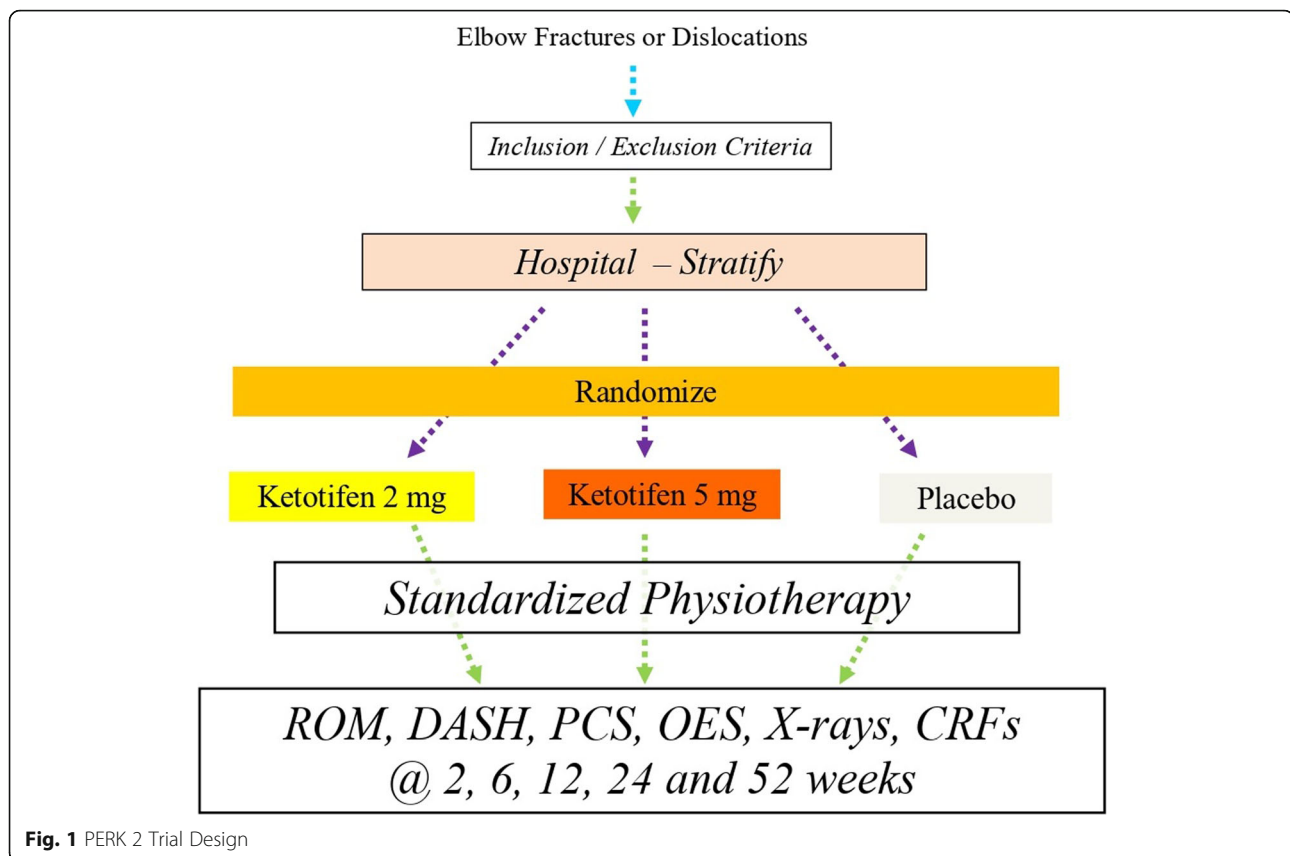
Methods/design

Participants, interventions, and outcomes

Seventeen academic medical centres from Canada (fourteen) and the United States (three) will be participating in the trial (Appendix 1). The study population of interest are adults (defined as 18 years of age or older) with any combination of distal humerus, or proximal radius or ulna fractures, or elbow dislocations without pre-existing elbow arthritis or contractures (Table 1). A 7 day window from injury to starting medication is based on research indicating that the intervention is most effective if administered early in the healing process [15]. The exclusion criteria are broadly divided in those that predispose to elbow contracture (elbow specific), those that are consequences of using KF or lactose placebo (medication contraindications), and those that interfere with the ability follow the protocol (participant specific (Table 1)). Further, there is a lack of safety evidence for the use of KF during pregnancy or breast feeding.

Interventions

Eligible participants will be randomized in equal proportions to receiving KF 2 mg, KF 5 mg, or a PL. This trial follows from the feasibility PERK 1 RCT (Clinicaltrials.gov, NCT01902017) where a dose of 5 mg was used, which is larger than the recommended dose of Ketotifen for the treatment of chronic asthma (1–2 mg twice daily) [11]. In choosing the second dose, the higher end of the recommended dose (2 mg) was selected balancing the effectiveness to prevent contractures and decreasing the chance for side effects (sedation). The medications will be administered orally twice daily for a total of 6 weeks post-randomization. Ketotifen Fumarate is manufactured in 1-mg capsules by TEVA Canada. Bay Area Research Logistics (BARL, Hamilton, Ontario, Canada) specializes in clinical trial medication packaging and distribution and will ensure blinding is achieved by over-encapsulation of each treatment, such that KF and PL capsules will appear identical. Ketotifen Fumarate is an antihistamine and sedation has been reported in 14% of people taking it in post-marketing surveillance [16]. Modifications to the allocated treatment will include discontinuing the capsules for serious suspected adverse reactions such as excessive drowsiness or skin rashes. Adherence to taking the medications will be stressed at the time of dispensing the capsules and reinforced through weekly calls by research personnel, as well as daily diarizing by participant. Adherence assessments with pill counts will be completed at the 2- and 6-week follow-up visits. A relatively short six-week medication administration will facilitate adherence. The only restricted medication that may not be taken simultaneously with KF is antihistamines. If these are required in the first 6 weeks



after randomization, the trial medication will be discontinued. There are no rescue medications for KF.

Assignment of interventions

Screening, randomization and enrollment is organized through the Epidemiology Coordinating and Research

Centre (EPICORE) at the University of Alberta. A stratified block randomization scheme by hospital site will be used to assign eligible participants at baseline to KF 2 mg, KF 5 mg, or PL in a 1:1:1 ratio using a computer-generated randomization scheme (i.e. conducted on REDCap over the internet via a desktop computer or a

Table 1 Eligibility Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Adults (≥ 18 years or older); skeletally mature - Injury to the elbow with any of the following: - Distal 1/3 humerus fracture (AO/OTA Type 13) - Proximal 1/3 ulna fracture (AO/OTA Type 2 U1) - Proximal 1/3 radius fracture (AO/OTA Type 2 R1) - Elbow dislocation - Open fractures with/without nerve injury <i>can</i> be included - Participant presents within 7 days or less between injury and trial recruitment - Participant requires operative treatment of the fracture - Participant has a negative urine pregnancy test	- Elbow specific - Pre-existing elbow contracture, osteoarthritis, inflammatory arthritis, gout or non-specific monoarticular arthritis of the injured elbow - Inability to mobilize elbow injury within 21 days of injury or surgery - Total Elbow for fracture treatment - Prior Elbow injury or surgery - Bilateral elbow fractures and / or dislocations - Medication contraindications - Oral hypoglycemic medications - History of epilepsy - Lactose intolerance - Any female who is pregnant or nursing - Severe hepatic impairment - Severe renal impairment - Male or female of reproductive age unwilling to use 2 methods of contraception - Participant specific - Unable to maintain follow-up (no fixed address, plans to move out of town in the next year, states unable to comply with protocol, etc...) - Has cognitive impairment or language difficulties that would impede the reliable completion of questionnaires - Concomitant musculoskeletal or visceral injuries preventing elbow physiotherapy - Unwilling or Unable to provide written informed consent.

web-enabled smart phone) in randomly assigned block sizes of 3, 6 or 9. All participants, care providers, research personnel, investigators, outcome assessors and data entry personnel will be blinded to intervention groups. Emergency unblinding will be permitted.

Outcomes

The primary outcome is the range of motion (ROM) in the flexion-extension arc and forearm pronation-supination arc obtained with a hand-held goniometer. Loss of ROM is a major reason for patients to consult physicians following elbow injury. Secondary outcomes include patient reported outcomes measures (PROMs) such as the Disability of the Arm, Shoulder, and Hand questionnaire (DASH), Pain Catastrophizing Scale (PCS) and Oxford Elbow Score (OES). The upper extremity scoring scale DASH is a validated 30-item PROM tool for disorders of the elbow with a range from 0 (least disability) to 100 (most disability). The PCS is a 13-item PROM with aggregates into three subscale scores assessing rumination, magnification, and helplessness that are combined into an overall score that range between 0 (no pain) and 42 (catastrophizing pain) [17–20]. PCS has been used in the assessment of injuries to the elbow, wrist, and hand where results were dependent on these behaviors. The OES is a 12-item valid measure of the outcome of elbow surgery in English and Dutch languages [21, 22]. There are three domains which include elbow function, pain, and social-psychological with values ranging from 0 (greatest severity) to 100 (least severity). The OES has been used in trauma populations [23–26]. It was reported that the OES performed well in assessing elbow surgical outcomes while the DASH was not responsive enough to warrant its exclusive use as an outcome of elbow surgery [27]. The other secondary outcomes include safety (adverse events (AE) and serious adverse events (SAE)), re-operations and fracture healing. For AE, SAE and re-operation, we are interested in the description and number of occurrence, while for fracture healing, our interest is the number of participants with disappearance of radiographic fracture lines overtime.

Data collection

Potential participants will be identified when scheduled for an operation for their injured elbow through the emergency department, hospital admission, or at an outpatient clinic. The surgeons will be involved in introducing the participants to the trial, discuss the potential concern regarding elbow contracture and the importance of preventing this disabling complication. Surgeons will also obtain permission from the participant for research personnel to contact the participant. Eligible participants who sign informed consent will be allocated to one of the three treatment arms and begin taking the medication the same day (Table 2). Participant assessments include standardized

phone calls at 1, 3, 4 and 5 weeks post-randomization to review medication use, ask about adverse events and confirm clinic appointments. Clinic visits, where ROM, PROMs, X-rays, and survey for adverse events are completed, occur at 2, 6, 12, 24 and 52 weeks post-randomization. X-rays will be gathered and stored at the Calgary Image Processing and Analysis Centre (4 views, including obliques). The presence or absence of visible fracture line to indicate healing and location of heterotopic ossification will be adjudicated by 3 independent reviewers. Pill counts will be performed at the 2- and 6-week followup visits (Table 2).

Sample size calculation

The sample size was estimated based on analysis of covariance model (ANCOVA) with respect to the mean change from baseline (as represented by the injured elbow at 2-week follow up visits) to flexion-extension arc of motion at week 12, on the basis of a two-sided test at the 0.05 α -level. A total of 702 participants (≈ 234 participants per arm) is needed to achieve about 95% power to detect a minimum improvement of 10 degrees among the treatment arms, assuming a standard deviation of 19.81, and an overall dropout rate of 11%. This sample size will have about 99.1% statistical power to detect a MCID in mean change (i.e. 10) in DASH scores [28] across treatment groups between baseline and week 12. Furthermore, the total sample size of 702 participants will ensure that we have at least 98% power to detect a minimum of 20% difference in the proportion of participants achieving functional flexion-extension arc of motion between placebo and treatment arms where a functional elbow ROM is defined as at least 30° – 130° flexion-extension arc for activities of daily living [29]. Seventeen centres will provide participants for the trial. The 13 sites outside of Calgary are forecasted to enroll 30 participants each and the 4 Calgary centres are forecast to enroll the remaining 312 participants (Appendix 1).

Statistics analysis

Descriptive analysis will be used to summarize ROM measurements, PROMs, safety (AE and SAE), re-operation and radiographic fracture healing. The analysis will follow the intention- to-treat protocol. Analysis of covariance (ANCOVA) will be used to model the impact of KF on ROM (change in 2 and 12 weeks of the injured elbow) adjusting for sex, age, injury classification and site. Similar analysis will be used to assess the impact of KF on in DASH, PCS and OES at 12 weeks, adjusting for these covariates. Mixed-effects regression analysis (effect of time) will be used to examine the impact of KF on changes in ROM and PROMs, adjusting for the earlier covariates. Logistic regression will be used to examine the impact of KF on radiographic fracture line disappearance (i.e. healing)

Table 2 Schedule of enrolment, interventions, and assessments

	TRIAL PERIOD											
	Enrolment	Allocation	Post-allocation (weeks)									
TIMEPOINT	0	0	0	1	2	3	4	5	6	12	24	52
ENROLMENT:												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
INTERVENTIONS:												
Medication												
Telephone reminder				X		X	X	X				
ASSESSMENTS:												
Pregnancy test	X											
Pill counts					X				X			
ROM					X				X	X	X	X
DASH	X				X				X	X	X	X
PCS	X				X				X	X	X	X
OES	X				X				X	X	X	X
CRF	X				X				X	X	X	X
Xray	X				X				X	X	*	*

* If indicated for delayed or nonunion

^a If indicated for delayed or nonunion

adjusting for sex, age, NSAID, smoking status. Sensitivity analysis will be used to evaluate the robustness of study findings to different methods for handling missing data [30]. Specifically, we will compare study conclusions based on complete data analysis, available data analysis, and use of multiple imputation based on Monte Carlo Markov Chain approach that adjusts for site, age and sex. Exploratory subgroup analyses to confirm treatment effect using different covariates such as range of motion (ROM), sex, age, side of injury is the same as dominant hand, race, concurrent injury and PROM i.e. DASH and OES.

Data monitoring

The Data Monitoring Committee (DMC), which will be formed, consist of an orthopaedic surgeon, clinical trialist and biostatistician but not involved with the proposed clinical trial in any manner and will be independent of the sponsor. Data will be reviewed twice yearly by the DMC via teleconference including recruitment and follow-up visit rates, SAEs, and descriptive statistics of the baseline demographics. Reports from the DMC will go to the Trial Steering Committee (TSC). The planned interim analysis will be shared with the DMC and a meeting arranged via teleconference for discussion and recommendations with the TSC. An interim analysis will be conducted when 50% of the participants have completed the primary outcome measure (ROM at the week 12 assessment). The DMC will evaluate whether there is an increased risk of KF use compared with PL. The parameters determined a priori to discontinue the trial include:

1. Greater than two times fatal or life-threatening SAEs that are Definitely or Probably related to KF (use Suspected Unexpected Serious Adverse Reaction SUSAR).
2. Greater than three times difference in the DASH and OES between groups.
3. Greater than three times the number of participants with non-functional ROM (30 degrees to 130 degrees flexion-extension arc) between groups.

If any one of the above criteria are met, the DMC will recommend to the TSC that the trial will be terminated prior to completion. The Trial Steering Committee (TSC) will include the Principal Investigator, Trial Biostatistician, Project Manager, Orthopaedic Clinical Trialist, and three site Principal Investigators or Project Managers. The TSC will meet quarterly to review trial performance and adjust the RCT as required based on safety and performance inputs. All outcome measures will be evaluated at the completion of the trial when the last participant has reached 52 weeks post-randomization.

Participant care

Concomitant care covers operations, medications, and rehabilitation/splints. Together, the participant and surgeon will determine the type of operation. This management will not be randomly assigned, but determined by injury characteristics. The operation can be performed before or after randomization; however randomization and first dose administration must occur within 7 days of injury. Analgesia may be provided by acetaminophen, opioids and/ or NSAID as required. Antihistamines use will be excluded for the 6 weeks that participants are taking trial medication since KF is an antihistamine. If possible, a local physiotherapist will direct a standardized home therapy program for all participants consisting of active ROM exercises performed three times per day with 20 repetitions for elbow flexion-extension arc and forearm pronation-supination arc. Progress will be monitored and adherence to home therapy will be reinforced every 2 weeks during the clinic visitation to the local physiotherapist. Stretching splints are instituted once it is clear that physiotherapy alone is insufficient, which occurs a minimum of 12 weeks post-randomization.

Safety

For the purposes of this trial, AEs will be defined as any unfavourable medical occurrence that a participant experiences, including sign, symptom or disease that occurs during participation in the trial whether or not considered trial medication related [7, 8, 28, 31–36]. Serious Adverse Events will be defined as any untoward medical occurrence that: results in death or is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; leads to persistent or significant disability and/or incapacity; causes a congenital anomaly and/or birth defect. All AEs and SAEs will be collected as a secondary outcome of the trial in a standardized format on the case report forms (CRFs). Suspected Adverse Reaction (SAR) is a type of AE where there is a reasonable possibility that the trial medication KF caused the AE. For all AEs, a temporal relationship will be observed in relation to the KF administration. Ketotifen Fumarate is administered over 6 weeks, and a 1-week washout period will be included. Thus, to be considered a SAR, the AE would have to occur within 7 weeks of randomization. The “definitely related” and “probably related” designations would indicate the AE is a SAR. For pregnancy, any conception that arises within the 6 weeks and/or within a 3-month interval after the 6-week course of KF will be followed to ascertain whether any birth defects, congenital anomalies or loss of pregnancy occurred. Unblinding will occur in order to ascertain what the participant was randomized in order

to provide counselling on what the fetus may have been exposed to KF or PL [31–35, 37–40]. All AEs or SAEs will be classified as expected or unexpected. Expected AEs are defined in the product monograph (PM) for KF and include recognized complications of an elbow fracture population undergoing an operation for the injury [36]. Unexpected AEs or SAEs are all other AEs or SAEs not defined as expected. Suspected unexpected serious adverse reactions (SUSAR) are defined as unexpected SAEs where there is causal relation between the SAE and use of KF.

Discussion

Currently, if contractures develop then only solution is an operation followed by 6–9 months of rehabilitation. An oral medication used during the recovery from the original injury to prevent post-traumatic contractures is a simpler and safer approach. Contractures complicate other orthopaedic conditions or procedures and positive results in post-traumatic contractures in elbow may warrant study of the use of KF in preventing contractures in other orthopaedic conditions or procedures. Therefore, we believed that the PrEvention of Posttraumatic Joint contractures With Ketotifen 2 (PERK 2) trial will provide evidence for a treatment (Ketotifen) to prevent contractures following joint injuries. If an improvement in ROM is observed, the treatment will have a significant impact on quality of life. A multi-centre design involving seventeen sites is planned to achieve a recruitment rate of 234 participants per year over 3 years to obtain a total of 702 participants. The multi-dosage regimen will provide an opportunity to determine the optimal dosage for treatment. The safety of KF for a new indication will be assessed, including radiographic fracture healing.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12891-020-3139-2>.

Additional file 1. Trial Sites.

Acknowledgements

Not applicable.

Authors' contributions

KAH:- Principal Investigator, Fund acquisition, study design, drafting and reviewing of manuscript. AA:- Draft, revision and submission of manuscript. PSS:- Study design and reviewing of manuscript, NM:- Review of manuscript, NJW:- Review of manuscript, MJB:- Review of manuscript, AG:- Review of manuscript, RAW:- Review of manuscript & TTS:- Review of manuscript. All authors have read and approved the final manuscript.

Funding

This grant for this trial was obtained from United States Department of Defense (Funding Reference Number: OR160026). According to the definition of funding, this is an externally funded, however, the funding body does not have any other role in this trial aside for the funding that was provided.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Ethics approval and consent to participate

The ethics approvals for the trial were obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary (REB 17-0609) and Institutional Review Board (IRB)/ Research Ethics Board (HSREB) of other participation sites. All Protocol modifications will be reported to IRBs/REBs, regulatory bodies and communicated to participating trial sites. In addition, we will obtain signed written consent from all participants before randomization in the study. On trial completion, the data will be migrated off the clinical trial data management platform and housed in research data archival service for a period appropriate to satisfy the regulatory and ethical requirements of the trial.

Consent for publication

Not applicable. The manuscript does not have any patient information or details.

Competing interests

There is no competing interest in the trial, however, the funding for the trial was obtained from the US Department of Defense. The funding body does not have any other role in this trial.

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PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

August 2020 Edition, Vol. 2

GOALS

By August 31st:

- Restart recruitment at capable active sites
- Restart regulatory procedures for new sites

MILESTONES

#1: Current enrollment status:



- Peter Lougheed Centre (n=14)
- South Health Campus (n=14)
- Sturgeon Community Hospital (n=7)
- Foothills Medical Centre (n=5)
- University of Vermont Medical Center (n=3)
- University of Maryland Medical Center (n=2)
- The Ottawa Hospital, Civic Campus (n=1)
- The Ottawa Hospital, General Campus (n=1)
- St. Michael's Hospital (n=0)
- St. Paul's Hospital (n=0)
- St. Joseph's Hospital (n=0)

TRIAL UPDATES

- We have **47** participants enrolled in the trial!
- **University of Vermont Medical Center** has **recruited** their first participant since COVID 19 restrictions were lifted by Sponsor on June 30th, 2020.
- Sponsor team is working on restart procedures for PERK 2 activities. Contact us if your site is able to restart.
- Coordinating Centre's REB approved ICF changes, including COVID-19 advisory information. Changes are under review by HRPO and will be distributed to sites once approved.
- The next **Trial Management Group** meeting with active sites is scheduled for **Monday, August 31st, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT).**

PERK 2 TEAM

Trial PI/Sponsor: Kevin Hildebrand

Research Coordinator: Gerardo Duque

Research Assistant: Taylor Stranaghan

PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

July 2020 Edition, Vol. 2

GOALS

By July 31st:

- Restart recruitment at capable active sites
- Restart regulatory procedures for new sites

MILESTONES

#1: Current enrollment status:



- Peter Lougheed Centre (n=14)
- South Health Campus (n=13)
- Sturgeon Community Hospital (n=7)
- Foothills Medical Centre (n=5)
- University of Maryland Medical Center (n=2)
- University of Vermont Medical Center (n=2)
- The Ottawa Hospital, Civic Campus (n=1)
- The Ottawa Hospital, General Campus (n=1)
- St. Michael's Hospital (n=0)
- St. Paul's Hospital (n=0)
- St. Joseph's Hospital (n=0)

TRIAL UPDATES

- We have **45** participants enrolled in the trial!
- Screening/Recruitment has restarted at all Calgary based sites (PLC, SHC, & FMC) and University of Vermont Medical Center.
- **Peter Lougheed Centre (PLC) has recruited the first participant since COVID 19 restrictions were lifted by Sponsor on June 30th, 2020.**
- Sponsor team is working on restart procedures for PERK 2 activities. Contact us if your site is able to restart.
- **Health Canada issued NOL for Protocol V5.0 amendment. Changes to ICF under review at coordinating site. To be distributed once approved.**
- The next **Trial Management Group** meeting with active sites is scheduled for **Monday, July 27th, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT).**

PERK 2 TEAM

Trial PI/Sponsor: Kevin Hildebrand

Research Coordinator: Gerardo Duque

Research Assistant: Taylor Stranaghan

PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

September 2020

Edition, Vol. 2



GOALS

By September 30th:

- Restart recruitment at capable active sites
- Restart regulatory procedures for new sites

MILESTONES

#1: Current enrollment status:



- Peter Lougheed Centre (n=14)
- South Health Campus (n=14)
- Sturgeon Community Hospital (n=7)
- Foothills Medical Centre (n=5)
- University of Vermont Medical Center (n=3)
- University of Maryland Medical Center (n=2)
- The Ottawa Hospital, Civic Campus (n=2)
- The Ottawa Hospital, General Campus (n=1)
- St. Michael's Hospital (n=0)
- St. Paul's Hospital (n=0)
- St. Joseph's Hospital (n=0)

TRIAL UPDATES

- We have **48** participants enrolled in the trial!
- **The Ottawa Hospital, Civic Campus has recruited their first participant since COVID 19 restrictions were lifted by Sponsor on June 30th, 2020.**
- Sponsor team is working on restart procedures for PERK 2 activities. Contact us if your site is able to restart.
- **Recent ICF and Drug Information Sheet changes approved by all regulatory agencies. Sites to submit to REB and send approval to coordinating center for HRPO submission.**
- The next **Trial Management Group** meeting with active sites proposed for **Monday, September 28th, 2020 at 1:00pm MDT (12:00pm PDT, 3:00pm EDT).**

PERK 2 TEAM

Trial PI/Sponsor: Kevin Hildebrand
Research Coordinator: Gerardo Duque
Research Assistant: Taylor Stranaghan