AWARD NUMBER: W81XWH-17-1-0665

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

PRINCIPAL INVESTIGATOR: Kevin A. Hildebrand

CONTRACTING ORGANIZATION: University of Calgary
Calgary, T2N1N4

REPORT DATE: October 2019

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCTOBER 2019	Annual	30SEP2018 - 29SEP2019

4. TITLE AND SUBTITLE
Prevention of Posttraumatic Contractures with Ketotifen II (PERK2)

5a. CONTRACT NUMBER
W81XWH-17-1-0665

5b. GRANT NUMBER
OR160026

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)
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 10 participating sites. Remaining 7 sites are poised for imminent approval. Nine of the participating sites have received ethics approval in addition to all Calgary lead sites. Site initiation visits were completed at 6 sites, with 3 actively recruiting and 3 with prospective start dates during Q1 of Year 3. Bay Area Research Logistics (BARL) has completed shipment of medication to all active and close to active sites. The Epidemiology Coordinating and Research Centre (EPICORE) at the University of Alberta organized screening, randomization and enrolment procedures, including the coordination of medication distribution between local sites and BARL using a custom program called Drug Tracking System (DTS). In addition, EPICORE is using the FDA compliant RedCap as the electronic data capturing system. These efforts have led to active sites successfully recruiting and randomizing 9 participants. Hiring and transition to a new coordinator supporting regulatory, budget, data and trial coordinating functions has been achieved. Site contract negotiations have been completed at 13 sites, with the remaining four to be done during Q1 of Year 3. Site training sessions were completed in June and September 2019. Charters for Data Monitoring Committee (DSMB), Trial Steering Committee (TSC), and Trial Management Group (TMG) were developed. Two abstracts for presentation and one manuscript drafts in development for publication.

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	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	Unclassified	539	USAMRMC
Unclassified	Unclassified	Unclassified			19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Table of Contents

Page

1. **Introduction……4**
2. **Keywords……4**
3. **Accomplishments……..4**
4. **Impact……..9**
5. **Changes/Problems..……..10**
6. **Products……..11**
7. **Participants & Other Collaborating Organizations……12**
8. **Special Reporting Requirements……14**
9. **Appendices……15**

1. INTRODUCTION:

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:

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. Establish an electronic data capturing method; a study randomization process linked with the supply of medication procurement, manufacturing and distribution center.
    b. Complete contract negotiations with recruiting sites.
    c. Obtain Ethics Internal Review Board and Department of Defense Human Research Protection Office (HRPO) approval for 17 participating sites.

3. Results:
    a. The Epidemiology Coordinating and Research Centre (EPICORE) at the University of Alberta has implemented an electronic data capture method using the FDA compliant REDCap that incorporates a central web based randomization process linked to the local site pharmacies and the central manufacture and distribution center for the study pills. **See appendices pages 16 – 17**.
    b. The same system will work serve as the gateway for coordination of medication distribution between local sites and BARL using a custom program called Drug Tracking System (DTS). **See appendices page 19**.
    c. Contracts completed and signed off for the following sites. **See appendices pages 20 – 268**:
        i. Sturgeon Community Hospital
        ii. University of Maryland Medical Center
        iii. South Health Campus
        iv. Rockyview General Hospital
        v. McGill University Health Centre
        vi. Foothills Medical Centre
        vii. St. Michaels Hospital
        viii. The Ottawa Hospital, Civic Campus
        ix. The Ottawa Hospital, General Campus
        x. St. Paul's Hospital
        xi. Queen Elizabeth II Health Science Center
    d. Ethic board approvals were received for the following sites. **See appendices pages 269 – 283:**
        i. University of Vermont Medical Centre
        ii. The Ottawa Hospital, Civic Campus
        iii. The Ottawa Hospital, General Campus
        iv. South Health Campus
        v. Sturgeon Community Hospital
        vi. University of Maryland Medical Centre
        vii. St. Paul's Hospital
        viii. Foothills Medical Centre
        ix. St. Michael's Hospital
        x. St. Joseph's Hospital
    e. Human Research Protection Office (HRPO) submission approvals were received for the following sites. **See appendices pages 284 - 308:**
        i. Carolinas Medical Center
        ii. South Health Campus
        iii. Sturgeon Community Hospital
        iv. Foothills Medical Centre
        v. University of Vermont Medical Centre
        vi. The Ottawa Hospital, Civic Campus
        vii. The Ottawa Hospital, General Campus
        viii. University of Maryland Medical Center
        ix. St. Michaels Hospital

Major Task 2: Phase III RCT Implementation

1. Major Activities:
    a. Organizational Transitions
    b. Site Initiations
    c. Organizing Screening, Enrollment and Randomization Procedures
    d. On-site monitoring
2. Specific Objectives:
    a. Hiring of new clinical research coordinator to address regulatory, budget, data and trial coordinating functions
    b. Start at Calgary Sites
    c. Roll out to sites outside of Calgary
    d. Monitor site performance and compliance
3. Results:
    a. Alexandra Garven, research coordinator, resigned effective June 30th, 2019. Replacement research coordinator, Gerardo Duque, was hired with a July 10th, 2019 start date. **See appendices pages 309 - 310**.
    b. Site initiation visits completed at the following sites. **See appendices pages 311 - 320**:
        i. Foothills Medical Centre
        ii. South Health Campus
        iii. Sturgeon Community Hospital
        iv. St. Michael's Hospital
        v. University of Maryland Medical Center
    c. First Participant recruited June 29, 2019 at the Peter Lougheed Centre, Calgary. **See appendices page 17**.
    d. First participant recruited July 2, 2019 at South Health Campus, Calgary. **See appendices page 17**.
    e. Following site initiations visits, official enrolment and randomization procedures started at Peter Lougheed Centre, South Health Campus. As a result, 9 participants have been recruited and randomized into the clinical trial. Appendix reflects 9 participants randomized by the end of the reporting period. Current total is 13 with enrolments occurring during October, 2019. **See appendices page 17**.
    f. Monitor Jackie Busheikin contracted and monitoring plan developed. First monitoring visit scheduled at Peter Lougheed Centre October 16th, 2019. South Health Campus monitoring meeting has been scheduled for the month of November, 2019. **See appendices pages 321 - 346**.

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, Trial Steering Committee, Trial Management Group were developed. **See appendices pages 347 - 380**.
    b. Two Trial Management Group meetings were held in 2019. **See appendices pages 381 - 385**.
    c. Ongoing communications with BARL to process and distribute drug to active sites. **See appendices pages 386 - 388**.
    d. Ongoing meeting with EPICORE for database development and completion. **See appendices pages 389 - 391**.
    e. October 9th CIPAC Meeting – **See appendices pages 392 - 400**.

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. Two abstracts coauthored by the graduate student on the grant, Ayo Ademola, presented at the Society for Clinical Trials annual meeting May 19 – 22, 2019. **See appendices pages 401 - 412**.
    b. Three manuscripts coauthored by the graduate student Ayo Ademola in draft preparation. **See appendices pages 413 - 481.**
    c. PERK 2 presentations at the Canadian Orthopaedic Trauma Society (COTS) meeting Montreal, QC in June and Denver, CO in September, 2019, and PERK 2 Investigator meeting in Montreal, QC June 20, 2019. **See appendices pages 482 - 524**.
    d. Monthly newsletter started March 2019, **See appendices pages 525 - 531**.

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 presenting 2 abstracts at the Society for Clinical Trials and writing the protocol manuscript drafts and the PERK 1 manuscript submitted to the Journal of Orthopaedic Trauma. **See appendices pages 401 - 412**.

Professional Development: - **See appendices pages 532 - 539**.

Kevin Hildebrand
- Sabbatical September 1, 2018 – August 31, 2019.
- Visiting Academic Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences University of Oxford, Oxford, UK September 1, 2019 – November 30, 2018.

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 continue steady recruitment at 3 active sites, with subsequent start of 3 more sites at the beginning of Year 3, Quarter 1. Also, start recruitment at 6 further sites by end of Year 3, Quarter 1. In regards to regulatory compliance leading to site start-ups, our objective is to complete all procedures involved for the 5 remaining sites by Year 3, Quarter 2. Continuing the TMG, TSC and DMC up and running. Regular meetings with the support organizations CIPAC, BARL, and EPICORE. Finally, submit protocol manuscript, with eyes set in further literature development efforts towards Year 3, 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

A project change report was submitted October 31, 2018. Personnel changes included a restructuring the 1.5 FTE administration staff from 3 to 2 individuals and site PI changes at 2 institutions. Another site was added. A recruitment update was submitted to accommodate the new site and to reflect delays in database development. Protocol modifications were expanding the population to include multiply injured individuals, Urine pregnancy screen at randomization, two methods of contraception, Range of motion to start within 3 weeks of injury, Collection of race at screening, allowing French and Spanish speaking participants, addition of the pain catastrophizing scale (PCS), and Total Elbow arthroplasty as an exclusion.

The announcement by Alexandra Garven May 10, 2019 of her resignation June 30, 2019, with last day of work June 14, 2019 presented a serious challenge. Her role included getting all sites through the ethics, DoD-HRPO, Health Canada, FDA and subsite contract approvals. We were able to get 2 sites up and recruiting by the end of this reporting period, but the other sites were delayed. After an interviewing process, Gerardo Duque accepted the position as Research Coordinator for PERK 2 to replace Alexandra.

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

There was a significant delay in the recruitment of the first participant on June 29, 2019. The major issue was support for database development, randomization scheme, and a drug tracking system. We had engaged the Clinical Research Unit (CRU) at the University of Calgary. With the system developed and plans to start recruiting December 2018, they presented an updated budget reflecting an additional $126,000 / yr over 4 years, or $504,000 on top of a budget of close to $200,000 in the negotiated contract between the University of Calgary and the US DoD. After spending time in the winter of 2019, a satisfactory resolution could not be reached and we approached EPICORE at the University of Alberta. They built the database in an FDA 21 CFR compliant REDCap database, with a randomization process and drug tracking system. They were able to accommodate the randomization scheme of the first 90 doses of medication we had shipped out to Calgary in late 2018 that had been ordered while working with CRU. The interruptions to our start in Calgary has caused some delays in the other sites as their IRB approvals have be modified with the change to EPICORE from the CRU. We are much happier with the EPICORE arrangement as it is more in line with our budget and they are very responsive to our needs with workable solutions.

Gerardo Duque has a large amount of work to move into the research coordinator role and assisting sites getting through the regulatory, ethics and contracts processes. Taylor Stranaghan is experienced with the site initiation visits and teaching the sites so that won't be a problem. Between July and September 2019 the team was able to complete regulatory processes and onboarding procedures for 7 sites – Sturgeon Community Hospital, Foothills Medical Centre, Carolinas Medical Centre, University of Maryland Medical Centre, The Ottawa Hospital – Civic & General sites, University of Vermont Medical Centre. Some sites have contractual final approvals to be confirmed. BARL estimates they will have medication ready to distribute to all sites listed as soon as they are ready to begin recruitment during Year 3, Quarter 1.

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.

Two abstracts coauthored by the graduate student on the grant, Ayo Ademola, presented at the Society for Clinical Trials annual meeting May 19 – 22, 2019. **See appendices pages 401 - 412**.

- **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:	orcid.org/0000-0001-8786-9021
Nearest Person Month worked:	3
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:	Alex Garven
Project Role:	Research Coordinator
Research Identifier:	None
Nearest Person Month worked:	5
Contribution to Project:	Regulatory application (IND, HRPO, Health Canada). Database development. Case report forms, consent. Assist in design and writing grants. Study Manager and randomization. Contracts. Institutional Review Board.
Funding Support:	Partial support from Department of Defense, Worker's Compensation Board of Alberta, Division of Orthopaedic Surgery, and Department of University of Calgary.
Name:	Taylor Stranaghan
Project Role:	Clinical Research Assistant
Research Identifier:	None
Nearest Person Month Worked:	12
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:	Gerardo Duque
Project Role:	Research Coordinator
Research Identifier:	None
Nearest Person Month worked:	2
Contribution to Project:	Regulatory application (IND, HRPO, Health Canada). Database Development and quality assurance. Case report forms and consent writing. Screening, recruitment, randomization, and participant follow ups. Contracts. Institutional Review Board processing.
Funding Support:	Department of Defense
Name:	Nicole Foldessy
Project Role:	Summer Student
Research Identifier:	None
Nearest Person Month worked:	2
Contribution to Project:	Database testing, brochures, manuals.
Funding Support:	Department of Defense
Name:	Tolulope Sajobi
Project Role:	Trial Statistician
Research Identifier:	orcid.org/0000-0002-5696-5552
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:

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments. **See appendices page 15**.

9. APPENDICES:

Prevention of Post-Traumatic Contractures with Ketotifen II (PERK II)
0R160026
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.

PERK 2

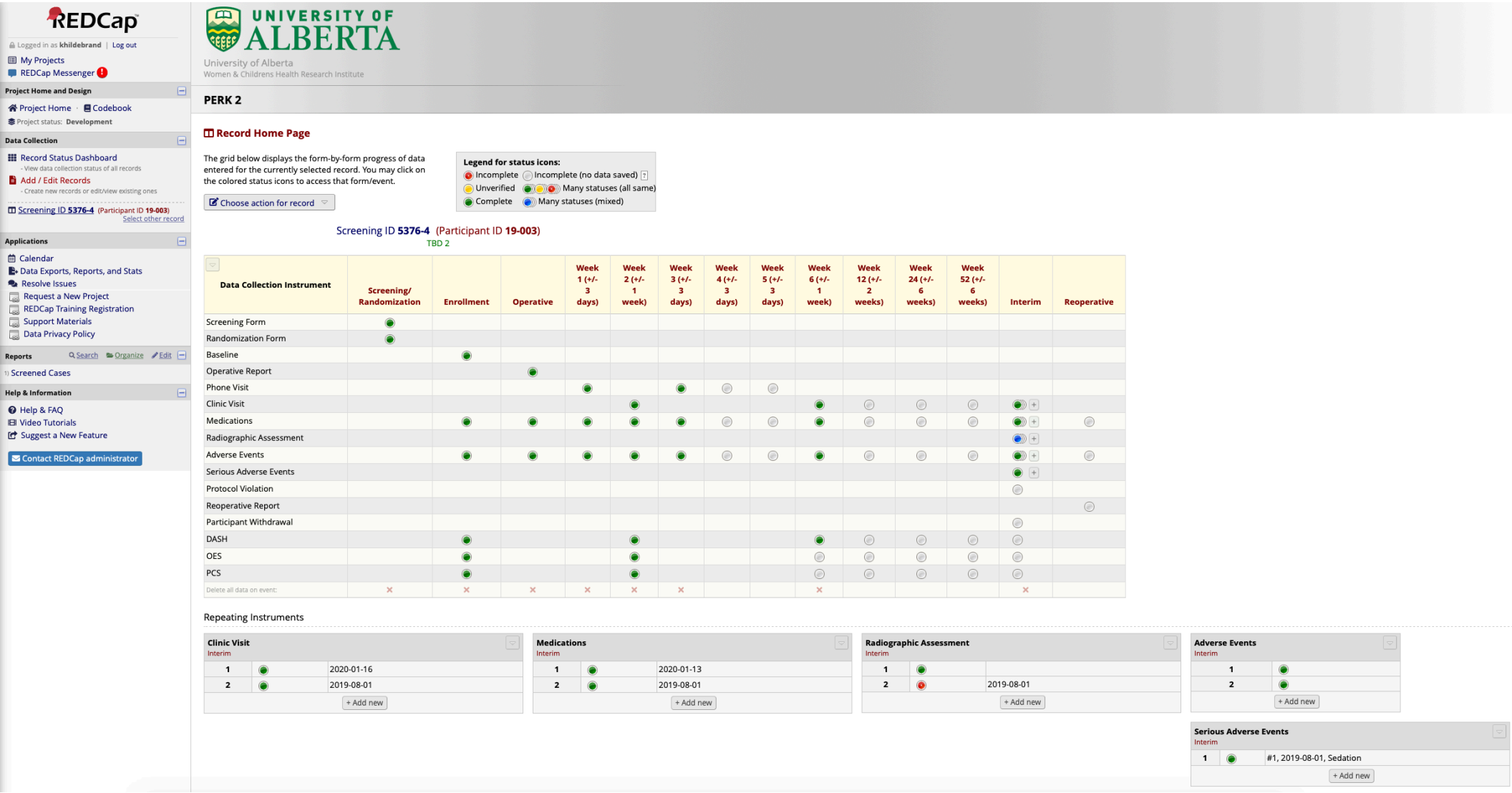
11 participants recruited by end of September, 2019 at two active sites. Third site began recruitment September, 2019. Change in Research Coordinator Central Coordinating center. EPICORE Database with screening, randomization and Drug tracking system capabilities completed. 7 more sites to start during Q1 of Year 3. Three publications to be submitted, including protocol manuscript.

Timeline and Cost

Activities CY	17	18	19	20
Complete CTDA				
Phase III RCT Implementation				
Study Performance				
Knowledge translation				
Estimated Budget ($K)	**$154**	**$638**	**$533**	**$000**

Updated: (October 28, 2019)

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
Delayed at this time due to challenges with database support
Budget Expenditure to Date
Projected Expenditure: $1,317,003
Actual Expenditure: $270,351


REDCap
Logged in as khildebrand | Log out
My Projects
REDCap Messenger
Project Home and Design
Project Home · Codebook
Project status: Development
Data Collection
Record Status Dashboard
- View data collection status of all records
Add / Edit Records
- Create new records or edit/view existing ones
Screening ID 5376-4 (Participant ID 19-003)
Select other record
Applications
Calendar
Data Exports, Reports, and Stats
Resolve Issues
Request a New Project
REDCap Training Registration
Support Materials
Data Privacy Policy
Reports
Search
Organize
Edit
1) Screened Cases
Help & Information
Help & FAQ
Video Tutorials
Suggest a New Feature
Contact REDCap administrator
UNIVERSITY OF ALBERTA
University of Alberta
Women & Childrens Health Research Institute
PERK 2
Record Home Page
The grid below displays the form-by-form progress of data entered for the currently selected record. You may click on the colored status icons to access that form/event.
Choose action for record
Legend for status icons:
Incomplete
Incomplete (no data saved)
Unverified
Many statuses (all same)
Complete
Many statuses (mixed)
Screening ID 5376-4 (Participant ID 19-003)
TBD 2
Data Collection Instrument
Screening/ Randomization
Enrollment
Operative
Week 1 (+/- 3 days)
Week 2 (+/- 1 week)
Week 3 (+/- 3 days)
Week 4 (+/- 3 days)
Week 5 (+/- 3 days)
Week 6 (+/- 1 week)
Week 12 (+/- 2 weeks)
Week 24 (+/- 6 weeks)
Week 52 (+/- 6 weeks)
Interim
Reoperative
Screening Form
Randomization Form
Baseline
Operative Report
Phone Visit
Clinic Visit
Medications
Radiographic Assessment
Adverse Events
Serious Adverse Events
Protocol Violation
Reoperative Report
Participant Withdrawal
DASH
OES
PCS
Delete all data on event:
Repeating Instruments
Clinic Visit
Interim
1 2020-01-16
2 2019-08-01
+ Add new
Medications
Interim
1 2020-01-13
2 2019-08-01
+ Add new
Radiographic Assessment
Interim
1
2 2019-08-01
+ Add new
Adverse Events
Interim
1
2
+ Add new
Serious Adverse Events
Interim
1 #1, 2019-08-01, Sedation
+ Add new

REDCap

Logged in as **khildebrand** | Log out

My Projects

REDCap Messenger

Project Home and Design

Project Home · Codebook

Project status: **Production**

Data Collection

Record Status Dashboard

Add / Edit Records

Applications

Calendar

Data Exports, Reports, and Stats

File Repository

Resolve Issues

Request a New Project

REDCap Training Registration

Support Materials

Data Privacy Policy

Reports Search | Organize | Edit

1) Screened Participants
2) Randomized Participants
3) Randomized Participants

Help & Information

Help & FAQ

Video Tutorials

Suggest a New Feature

Contact REDCap administrator

UNIVERSITY OF ALBERTA

University of Alberta
Women & Childrens Health Research Institute

PERK 2 (PrEvention of posttraumatic contractuRes with Ketotifen 2)

Record Status Dashboard (all records)

Displayed below is a table listing all existing records/responses and their status for every data collection instrument (and if longitudinal, for every event). You may click any of the colored buttons in the table to open a new tab/window in your browser to view that record on that particular data collection instrument. Please note that if your form-level user privileges are restricted for certain data collection instruments, you will only be able to view those instruments, and if you belong to a Data Access Group, you will only be able to view records that belong to your group.

Legend for status icons:
- Incomplete
- Incomplete (no data saved)
- Unverified
- Complete

Dashboard displayed: [Default dashboard]

Displaying Data Access Group -- ALL --

Displaying record Page 1 of 1: "5251-1" through "5254-19" of **24** records ALL (24) records per page

+ Add new record

Displaying: Instrument status only | Lock status only | All status types

Screening ID	Baseline	
	SCREENING FORM	RANDOMIZATION FORM
5251-1		
5251-2		
5251-3		
5251-4 (Participant ID 01-001)		
5251-5 (Participant ID 01-002)		
5254-1		
5254-2 (Participant ID 05-0001)		
5254-3		
5254-4		
5254-5		
5254-6		
5254-7		
5254-8		
5254-9		
5254-10		
5254-11		
5254-12		
5254-13 (Participant ID 05-0002)		
5254-14		
5254-15		
5254-16		
5254-17		
5254-18		
5254-19		

UNIVERSITY OF ALBERTA

University of Alberta
Women & Childrens Health Research Institute

PERK 2

Data Exports, Reports, and Stats

VIDEO: How to use Data Exports, Reports, and Stats

+ Create New Report | My Reports & Exports | Other Export Options | View Report: Randomized Subjects

Number of results returned: 13
Total number of records queried: 332
('records' = total available data across all designated events)

Stats & Charts | Export Data | Print Page | Edit Report

Live filters: [Data Access Group]

Randomized Subjects

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
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
5358-56 (Participant ID 01-004)	Screening/ Randomization			Peter Lougheed Centre	10020	2019-09-11
5358-70 (Participant ID 01-005)	Screening/ Randomization			Peter Lougheed Centre	10012	2019-10-11
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
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
5362-39 (Participant ID 05-005)	Screening/ Randomization			South Health Campus	10050	2019-09-17
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

Drug Tracking System

Bottle ID Number	Participant ID	Assigned Expiry Date	Date Shipped	Received Date	Status	Returned	Disposed	
10001	1-002	29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Allocated	Yes	Yes	Save
10002		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10003		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10004		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10005		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10006	1-003	29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Allocated	Yes	Yes	Save
10007		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10008	1-001	29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Allocated	Yes	Yes	Save
10009		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10010		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10011		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save
10012	1-005	29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Allocated			Save
10013		29-Feb-2020	11-Apr-2019	dd-MMM-yyyy	Available			Save

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. Prism Schneider of Calgary, Alberta
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Alberta Health Services
10301 Southport Lane SW, Calgary, Alberta, Canada, T2W 1S7
(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").

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 INVESTIGATOR and the SUB INSTITUTION have agreed to participate in the Clinical Study.

WHEREAS the SUB INVESTIGATOR and PRINCIPAL INVESTIGATOR both have academic appointments at the PRINCIPAL INSTITUTION and shall perform the Clinical Study within the scope of those academic appointments;

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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical

records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon receipt of a request for inspection of the SUB INSTITUTION by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Clinical Study activities.

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the study drug Ketotifen 2 ("Study Drug") and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return all of the unused Study Drug to the PRINCIPAL INSTITUTION. In the event unused Study Drug is destroyed at the completion or early termination of the Clinical Study, SUB INSTITUTION will provide written confirmation of destruction of Study Drug to PRINCIPAL INVESTIGATOR.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision

to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation or for internal reporting purposes.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete

multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUB INSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to

keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for twenty-five (25) years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with

applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. PRINCIPAL INSTITUTION and SUB INSTITUTION shall each at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination

of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Prism Schneider C/O Tanja Harrison
Foothills Medical Centre – McCaig Tower
3134 Hospital Drive NW
Calgary, Alberta, Canada T2N 5A1
Phone: 403.944.4594
Email: tharriso@ucalgary.ca

to the SUB INSTITUTION:

Alberta Health Services
Legal & Privacy
10301 Southport Lane SW
Calgary, Alberta, Canada T2W 1S7
Attn: Mark Maxwell, Legal Counsel
Tel: (403) 210-6950

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ June 7, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ JUN 0 5 2019

Marcello Tonelli — Date

Senior Associate Dean, Clinical Research

SUB INVESTIGATOR:

Dr. Prism Schneider

Signature: _____ July 26 2019

Date

SUB INSTITUTION:

ALBERTA HEALTH SERVICES

Authorized Signatures: _____ June 5, 2019

Becky Wong — Date

Director, Health System Access

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description Study Coordinator	Indirect (39.8%)	Description Parking	Indirect (NA)	Description Beverage	Indirect (NA)	Description Pharmacy	Indirect (NA)	Year 1 Total
March 30, 2019-	1815.00	722.37	160.00	0	30.00	0	2,640.00	0	
June 30, 2019-	6,800.00	2706.4	720.00	0	130.00	0	300.00	0	
September 30, 2019-	8,550.00	3402.9	1,000.00	0	200.00	0	300.00	0	
December 30, 2019-	9,155.00	3643.69	1,060.00	0	210.00	0	330.00	0	
TOTAL	26,320.00	10,475.36	2,960.00	0.00	570.00	0.00	3,570.00	0.00	43,895.36

Year 2-2020

Payments to be made Quarterly	Description Study Coordinator	Indirect (39.8%)	Description Parking	Indirect (NA)	Description Beverage	Indirect (NA)	Description Pharmacy	Indirect (NA)	Year 2 Total
March 30, 2020-	10,155.00	7006.95	1220.00	0.00	250.00	0.00	1380.00	0.00	
June 30, 2020-	11,300.00	7797	1,440.00	0.00	310.00	0.00	300.00	0.00	
September 30, 2020-	11,050.00	4397.9	1,400.00	0.00	300.00	0.00	300.00	0.00	
December 30, 2020-	11,300.00	4497.4	1,440.00	0.00	310.00	0.00	300.00	0.00	
TOTAL	21,455.00	23,699.25	5,500.00	0.00	1,170.00	0.00	2,280.00	0.00	54,101.25

Year 3-2021

Payments to be made Quarterly	Description Study coordinator	Indirect (39.8%)	Description Parking	Indirect (NA)	Description Beverage	Indirect (NA)	Description Pharmacy	Indirect (NA)	Year 3 Total
March 30, 2021-	5,250.00	2089.5	840.00	0.00	210.00	0.00	1050.00	0.00	
June 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	0.00	0.00	
September 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	0.00	0.00	
December 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	1,500.00	0.00	
TOTAL	12,750.00	5,074.50	2,040.00	0.00	510.00	0.00	2,550.00	0.00	22,924.50

TOTAL BUDGET: $120,924.11 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

120,924.11

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q1	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q2	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 3 participants x $250/participant =	$750
			C$6,800
	Q3	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
			C$8,550
	Q4	Enrollment - 11 participants x $605/participant =	$6,655
		12 weeks – 10 participants x $250/participant =	$2,500
			C$9,155
Year 2020:	Q1	Enrollment - 11 participants x $605/participant =	$6,655
		12 weeks – 11 participants x $250/participant =	$2,750
		52 weeks – 3 participants x $250/participant =	$750
			C$10,155
	Q2	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 11 participants x $250/participant =	$2,750
		52 weeks – 10 participants x $250/participant =	$2,500
			C$11,300
	Q3	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 10 participants x $250/participant =	$2,500
			C$11,050
	Q4	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 11 participants x $250/participant =	$2,750
			C$11,300
Year 2021:	Q1	12 weeks - 10 participants x $250/participant =	$2,500
		52 weeks – 11 participants x $250/participant =	$2,750
			C$5,250
	Q2	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q3	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q4	52 weeks – 10 participants x $250/participant =	$2,500

C$2,500

Participant Parking:

Year 2019:	Q1	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q2	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 3 participants x $40/participant =	$120
			C$720
	Q3	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
			C$1,000
	Q4	Enrollment - 11 participants x $60/participant =	$660
		12 weeks – 10 participants x $40/participant =	$400
			C$1,060
Year 2020:	Q1	Enrollment - 11 participants x $60/participant =	$660
		12 weeks – 11 participants x $40/participant =	$440
		52 weeks – 3 participants x $40/participant =	$120
			C$1,220
	Q2	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 11 participants x $40/participant =	$440
		52 weeks – 10 participants x $40/participant =	$400
			C$1,440
	Q3	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 10 participants x $40/participant =	$400
			C$1,400
	Q4	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 11 participants x $40/participant =	$440
			C$1,440
Year 2021:	Q1	12 weeks - 10 participants x $40/participant =	$400
		52 weeks – 11 participants x $40/participant =	$440
			C$840
	Q2	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q3	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q4	52 weeks – 10 participants x $40/participant =	$400
			C$400

Participant Beverage/Food card:

Year 2019:	Q1	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q2	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 3 participants x $10/participant =	$30
			C$130
	Q3	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
			C$200

	Q4	Enrollment - 11 participants x $10/participant =	$110
		12 weeks – 10 participants x $10/participant =	$100
			C$210
Year 2020:	Q1	Enrollment - 11 participants x $10/participant =	$110
		12 weeks – 11 participants x $10/participant =	$110
		52 weeks – 3 participants x $10/participant =	$30
			C$250
	Q2	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 11 participants x $10/participant =	$110
		52 weeks – 10 participants x $10/participant =	$100
			C$310
	Q3	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 10 participants x $10/participant =	$100
			C$300
	Q4	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 11 participants x $10/participant =	$110
			C$310
Year 2021:	Q1	12 weeks - 10 participants x $10/participant =	$100
		52 weeks – 11 participants x $10/participant =	$110
			C$210
	Q2	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q3	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q4	52 weeks – 10 participants x $10/participant =	$100
			C$100

Investigational Drug Service

Year 2019:	Q1	Start Up Fee =	$1,500
		Maintenance Fee - =	$1,050
		Dispensing fee – 3 participants x $30/participant =	$90
			C$2,640
	Q2	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q3	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q4	Dispensing fee – 11 participants x $30/participant =	$330
			C$330
Year 2020:	Q1	Maintenance Fee - =	$1,050
		Dispensing fee – 11 participants x $30/participant =	$330
			C$1,380
	Q2	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q3	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q4	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
Year 2021:	Q1	Maintenance Fee - =	$1.050
			C$1,050

Q2	Maintenance Fee -	=	$0 C$0
Q3	Maintenance Fee -	=	$0 C$0
Q4	Close-out Fee	=	$1,500 C$1,500

H. INDIRECT COSTS

1. General & Administrative:

The rate at the Foothills Medical Centre is the University of Calgary rate, 39.8%. All salaries and wages, and fringe benefits are included in the calculation. The participant support costs such as parking and beverage/food cards, and the Investigational Drug Services, are not included.

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. Edward J. Harvey
The McGill University Health Centre
Montreal General Hospital
1650 Cedar Avenue Room B5.159.5
Montreal, Quebec H3G 1A4 Canada
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

The Research Institute of the McGill University Health Centre
2155 Guy Street, Suite 500
Montreal, Quebec H3H 2R9 Canada

(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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and/or the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to

PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the Study Drug and placebo, free of charge, in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB

INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: The Research Institute of the McGill University Health Centre

Address of Payee: Accounts Receivable
Finance Department
The Research Institute of the McGill University Health Centre
2155 Guy Street, Suite 500
Montreal, QC H3H 2R9
Tel: (514) 934-1934 ext. 71455
Email: accountsreceivable.rimuhc@muhc.mcgill.ca

Please identify all payments by including on the statement, the Name of the SUB INVESTIGATOR and the Protocol name or number.

2.3 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional

material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUBINSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, and at PRINCIPAL INSTITUTION'S expense, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada

regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta) and the *Act respecting Health Services and Social Services* (Quebec); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, officers or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION, in accordance with the SUB INSTITUTION's policies and procedures, excluding subject medical records which shall remain at all times the property of SUB INSTITUTION. SUB INSTITUTION and SUB INVESTIGATOR shall retain a non-exclusive, perpetual, fully paid-up license to use the IP for their own non-commercial academic, research, clinical and educational purposes.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. Each Party shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this

Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax, email or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Edward J. Harvey
The McGill University Health Centre
Montreal General Hospital
1650 Cedar Avenue Room B5.159.5
Montreal, Quebec H3G 1A4
Tel: 514 934-1934, ext. 42734
Email: edward.harvey@mcgill.ca

to the SUB INSTITUTION:

Cinzia Raponi CPA, CMA
General Director, Administration
The Research Institute of the McGill University Health Centre
2155 Guy Street, Suite 500 Montreal Quebec, Canada H3H 2R9
Tel: 514-934-1934 ext 44515
Fax: 514-934-8270
Email:cinzia.raponi@muhc.mcgill.ca

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary

Legal, Research Services - CSM

Office G360, Ground Floor Health Sciences Building

3280 Hospital Drive NW

Calgary, Alberta, Canada T2N 4Z6

Attn: Manager

Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner. Nothing in this Agreement shall be construed as creating solidarity between the SUB INSTITUTION and SUB INVESTIGATOR.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the home Province where the Party defendant in litigation is located and the federal laws of Canada applicable therein. The Parties further acknowledge that the courts of the home province of the Party defendant in the litigation shall have exclusive jurisdiction to entertain any complaint, demand, claim or cause of action whatsoever arising out of this Agreement and hereby irrevocably submit to the exclusive jurisdiction of said courts.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement

21. Language

The parties hereto acknowledge that they have requested that this Agreement be drafted in the English language. *Les parties reconnaissent avoir exigé que cette convention soit rédigée en anglais.*

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ July 10, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ JUL 09 2019

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____ July 4, 2019

Dr. Edward J. Harvey — Date

SUB INSTITUTION:

Authorized Signatures: _____ July 5, 2019

Costas N. Karatzas, M.Sc., Ph.D.
Director, Business Development and
Contracts Office — Date

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (28.4%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (28.4%)	
June 30, 2019	1,815.00	515.46	180.00	0	30.00	0	1,360.00	386.24	
September 30, 2019	3,170.00	900.28	360.00	0	70.00	0	350.00	99.4	
December 30, 2019	3,420.00	971.28	400.00	0	80.00	0	350.00	99.4	
TOTAL	8,405.00	2,387.02	940.00	0.00	180.00	0.00	2,060.00	585.04	14,557.06

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (28.4%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (28.4%)	
March 30, 2020	4,025.00	1143.10	460.00	0.00	90.00	0.00	460.00	130.64	
June 30, 2020	5,025.00	1427.10	620.00	0.00	130.00	0.00	400.00	113.60	
September 30, 2020	5,275.00	1498.10	660.00	0.00	140.00	0.00	400.00	113.60	
December 30, 2020	4,670.00	1326.28	600.00	0.00	130.00	0.00	350.00	99.40	
TOTAL	18,995.00	5,394.58	2,340.00	0.00	490.00	0.00	1,610.00	457.24	29,286.82

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (28.4%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (28.4%)	
March 30, 2021	2,250.00	639.00	360.00	0.00	90.00	0.00	150.00	42.60	
June 30, 2021	1,250.00	355.00	200.00	0.00	50.00	0.00	150.00	42.60	
September 30, 2021	1,250.00	355.00	200.00	0.00	50.00	0.00	150.00	42.60	
December 30, 2021	1,000.00	284.00	160.00	0.00	40.00	0.00	450.00	127.80	
TOTAL	5,750.00	1,633.00	920.00	0.00	230.00	0.00	900.00	255.60	9,688.60

TOTAL BUDGET: $53,532.48 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

[redacted]

[redacted]

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q3	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 3 participants x $250/participant =	$750
			C$3,170
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 4 participants x $250/participant =	$1,000
			C$3,420
Year 2020:	Q1	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 4 participants x $250/participant =	$1,000
			C$4,025
	Q2	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 3 participants x $250/participant =	$750
			C$5,025
	Q3	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$5,275
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$4,670
Year 2021:	Q1	12 weeks - 4 participants x $250/participant =	$1,000
		52 weeks – 5 participants x $250/participant =	$1,250
			C$2,250
	Q2	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q3	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q4	52 weeks – 4 participants x $250/participant =	$1,000
			C$1,000

Participant Parking:

Year 2019:	Q2	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q3	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 3 participants x $40/participant =	$120
			C$360
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 4 participants x $40/participant =	$160
			C$400
Year 2020:	Q1	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 4 participants x $40/participant =	$160
			C$460
	Q2	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 3 participants x $40/participant =	$120
			C$620
	Q3	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$660
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$600
Year 2021:	Q1	12 weeks - 4 participants x $40/participant =	$160
		52 weeks – 5 participants x $40/participant =	$200
			C$360
	Q2	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q3	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q4	52 weeks – 4 participants x $40/participant =	$160
			C$160

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q3	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 3 participants x $10/participant =	$30
			C$70
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 4 participants x $10/participant =	$40
			C$80
Year 2020:	Q1	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 4 participants x $10/participant =	$40
			C$90
	Q2	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 3 participants x $10/participant =	$30
			C$130

	Q3	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$140
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$130
Year 2021:	Q1	12 weeks - 4 participants x $10/participant =	$40
		52 weeks – 5 participants x $10/participant =	$50
			C$90
	Q2	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q3	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q4	52 weeks – 4 participants x $10/participant =	$40
			C$40

Investigational Drug Service (Using Dalhousie template)

Year 2019:	Q2	Start Up Fee	=	$1,000
		Maintenance Fee -	=	$150
		Dispensing fee – 3 participants x $50/participant =		$150
		Monitoring visit	=	$60
				C$1,360
	Q3	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
	Q4	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
Year 2020:	Q1	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
		Monitoring visit	=	$60
				C$460
	Q2	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
				C$400
	Q3	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
				C$400
	Q4	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
Year 2021:	Q1	Maintenance Fee -	=	$150
				C$150
	Q2	Maintenance Fee -	=	$150
				C$150
	Q3	Maintenance Fee -	=	$150
				C$150
	Q4	Maintenance Fee -	=	$150
		Close-out Fee	=	$300
				C$450

H. INDIRECT COSTS

1. General & Administrative:

The rate at the McGill University Health Centre is 28.4%. All salaries and wages, and applicable fringe benefits, and the Investigational Drug Service, are included in the calculation. Participant support costs such as parking and beverage/food cards are not included.

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. J. Andrew Trenholm
Department of Surgery
QEII Health Sciences Centre
1796 Summer Street, Room 4868
Halifax Nova Scotia
B3H 3A7

(the "SITE INVESTIGATOR")

OF THE THIRD PART,

-and-

Nova Scotia Health Authority
5790 University Ave.
Halifax, NS B3H 1V7
(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").

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 SITE INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SITE INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SITE INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SITE INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SITE INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SITE INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SITE INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SITE INVESTIGATOR's compliance with their obligations

herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SITE INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SITE INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SITE INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the study drug ("Study Drug") and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SITE INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SITE INVESTIGATOR will destroy or return any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SITE INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: Nova Scotia Health Authority

Address of Payee: 1796 Summer Street, Room 4810
Halifax, NS B3H 3A7
Attn: Kelly Trask

2.3 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SITE INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SITE INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation.

4. Publication

4.1 The SITE INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete

multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SITE INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SITE INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SITE INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SITE INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SITE INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUB INSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SITE INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SITE INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to

keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SITE INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SITE INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SITE INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SITE INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SITE INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SITE INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with

applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SITE INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. Each Party shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SITE INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SITE INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SITEINVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SITE INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SITE INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SITE INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination

of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:
Dr. J Andrew Trenholm
1796 Summer Street, Room 4868
Halifax, Nova Scotia
B3H 3A7

to the SUB INSTITUTION:
Nova Scotia Health Authority
Research and Innovation
5790 University Ave.
Halifax, NS B3H 1V7
Tel: 902-473-4841

to the PRINCIPAL INVESTIGATOR:
Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:
The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this

Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ October 21, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ OCT 2 3 2019

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SITE INVESTIGATOR:

Signature: _____ 10/09/2019

Date

SUB INSTITUTION:

Authorized Signatures: _____ Oct 18 2019

Dr. Gail Tombilin Murphy, PhD
Vice-President, Research and Innovation
Nova Scotia Health Authority

Date

Signature: _____ 10/11/2019

Victoria Sullivan
Central Zone Operations Executive Director

Date

Dr. Gail Tomblin Murphy, PhD
Vice-President, Research and Innovation
Nova Scotia Health Authority

Victoria Sullivan
Central Zone Operations Executive Director

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

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. Kelly Johnston of Calgary, Alberta
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Alberta Health Services
10301 Southport Lane SW, Calgary, Alberta, Canada, T2W 1S7
(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").

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 INVESTIGATOR and the SUB INSTITUTION have agreed to participate in the Clinical Study.

WHEREAS the SUB INVESTIGATOR and PRINCIPAL INVESTIGATOR both have academic appointments at the PRINCIPAL INSTITUTION and shall perform the Clinical Study within the scope of those academic appointments;

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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical

records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon receipt of a request for inspection of the SUB INSTITUTION by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Clinical Study activities.

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the study drug Ketotifen 2 ("Study Drug") and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return all of the unused Study Drug to the PRINCIPAL INSTITUTION. In the event unused Study Drug is destroyed at the completion or early termination of the Clinical Study, SUB INSTITUTION will provide written confirmation of destruction of Study Drug to PRINCIPAL INVESTIGATOR.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision

to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation or for internal reporting purposes.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete

multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUB INSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to

keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for twenty-five (25) years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with

applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. PRINCIPAL INSTITUTION and SUB INSTITUTION shall each at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination

of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Kelly Johnston C/O Saboura Mahdavi
Clinical Research Coordinator
335 – 401 9 Ave SW
Calgary, Alberta, Canada T2P 3C5
Tel: 403-265-4885
Email: mahdavis@ucalgary.ca

to the SUB INSTITUTION:

Alberta Health Services
Legal & Privacy
10301 Southport Lane SW
Calgary, Alberta, Canada T2W 1S7
Attn: Mark Maxwell, Legal Counsel
Tel: (403) 210-6950

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ June 7, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ JUN 05 2019

Marcello Tonelli — Date

Senior Associate Dean, Clinical Research

SUB INVESTIGATOR:

Dr. Kelly Johnston

Signature: _____ June 11, 2019.

Date

SUB INSTITUTION:

ALBERTA HEALTH SERVICES

Authorized Signatures: _____ June 5, 2019

Becky Wong — Date

Director, Health System Access

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
June 30, 2019	1,815.00	722.37	180.00	0	30.00	0	2,640.00	0	
September 30, 2019	3,170.00	1261.66	360.00	0	70.00	0	120.00	0	
December 30, 2019	3,420.00	1361.16	400.00	0	80.00	0	120.00	0	
TOTAL	8,405.00	3,345.19	940.00	0.00	180.00	0.00	2,880.00	0.00	15,750.19

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2020	4,025.00	1601.95	460.00	0.00	90.00	0.00	1200.00	0.00	
June 30, 2020	5,025.00	1999.95	620.00	0.00	130.00	0.00	150.00	0.00	
September 30, 2020	5,275.00	2099.45	660.00	0.00	140.00	0.00	150.00	0.00	
December 30, 2020	4,670.00	1858.66	600.00	0.00	130.00	0.00	120.00	0.00	
TOTAL	18,995.00	7,560.01	2,340.00	0.00	490.00	0.00	1,620.00	0.00	31,005.01

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2021	2,250.00	895.5	360.00	0.00	90.00	0.00	1050.00	0.00	
June 30, 2021	1,250.00	497.5	200.00	0.00	50.00	0.00	0.00	0.00	
September 30, 2021	1,250.00	497.5	200.00	0.00	50.00	0.00	0.00	0.00	
December 30, 2021	1,000.00	398	160.00	0.00	40.00	0.00	1,500.00	0.00	
TOTAL	5,750.00	2,288.50	920.00	0.00	230.00	0.00	2,550.00	0.00	11,738.50

TOTAL BUDGET: $58,493.70 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

58,493.70

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q3	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 3 participants x $250/participant =	$750
			C$3,170
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 4 participants x $250/participant =	$1,000
			C$3,420
Year 2020:	Q1	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 4 participants x $250/participant =	$1,000
			C$4,025
	Q2	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 3 participants x $250/participant =	$750
			C$5,025
	Q3	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$5,275
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$4,670
Year 2021:	Q1	12 weeks - 4 participants x $250/participant =	$1,000
		52 weeks – 5 participants x $250/participant =	$1,250
			C$2,250
	Q2	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q3	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q4	52 weeks – 4 participants x $250/participant =	$1,000
			C$1,000

Participant Parking:

Year 2019:	Q2	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q3	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 3 participants x $40/participant =	$120
			C$360
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 4 participants x $40/participant =	$160
			C$400
Year 2020:	Q1	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 4 participants x $40/participant =	$160
			C$460
	Q2	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 3 participants x $40/participant =	$120
			C$620
	Q3	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$660
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$600
Year 2021:	Q1	12 weeks - 4 participants x $40/participant =	$160
		52 weeks – 5 participants x $40/participant =	$200
			C$360
	Q2	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q3	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q4	52 weeks – 4 participants x $40/participant =	$160
			C$160

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q3	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 3 participants x $10/participant =	$30
			C$70
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 4 participants x $10/participant =	$40
			C$80
Year 2020:	Q1	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 4 participants x $10/participant =	$40
			C$90
	Q2	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 3 participants x $10/participant =	$30
			C$130

	Q3	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$140
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$130
Year 2021:	Q1	12 weeks - 4 participants x $10/participant =	$40
		52 weeks – 5 participants x $10/participant =	$50
			C$90
	Q2	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q3	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q4	52 weeks – 4 participants x $10/participant =	$40
			C$40

Investigational Drug Service

Year 2019:	Q2	Start Up Fee =	$1,500
		Maintenance Fee - =	$1,050
		Dispensing fee – 3 participants x $30/participant =	$90
			C$2,640
	Q3	Dispensing fee – 4 participants x $30/participant =	$120
			C$120
	Q4	Dispensing fee – 4 participants x $30/participant =	$120
			C$120
Year 2020:	Q1	Maintenance Fee - =	$1,050
		Dispensing fee – 5 participants x $30/participant =	$150
			C$1,200
	Q2	Dispensing fee – 5 participants x $30/participant =	$150
			C$150
	Q3	Dispensing fee – 5 participants x $30/participant =	$150
			C$150
	Q4	Dispensing fee – 4 participants x $30/participant =	$120
			C$120
Year 2021:	Q1	Maintenance Fee - =	$1,050
			C$1,050
	Q2	Maintenance Fee - =	$0
			C$0
	Q3	Maintenance Fee - =	$0
			C$0
	Q4	Close-out Fee =	$1,500
			C$1,500

H. INDIRECT COSTS

1. General & Administrative:

The rate at the Rockyview General Hospital is the University of Calgary rate, 39.8%. All salaries and wages, and fringe benefits are included in the calculation. The participant support costs such as parking and beverage/food cards, and the Investigational Drug Services, are not included.

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. Neil White of Calgary, Alberta
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Alberta Health Services
10301 Southport Lane SW, Calgary, Alberta, Canada, T2W 1S7
(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").

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 INVESTIGATOR and the SUB INSTITUTION have agreed to participate in the Clinical Study.

WHEREAS the SUB INVESTIGATOR and PRINCIPAL INVESTIGATOR both have academic appointments at the PRINCIPAL INSTITUTION and shall perform the Clinical Study within the scope of those academic appointments;

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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical

records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon receipt of a request for inspection of the SUB INSTITUTION by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Clinical Study activities.

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the study drug Ketotifen 2 ("Study Drug") and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return all of the unused Study Drug to the PRINCIPAL INSTITUTION. In the event unused Study Drug is destroyed at the completion or early termination of the Clinical Study, SUB INSTITUTION will provide written confirmation of destruction of Study Drug to PRINCIPAL INVESTIGATOR.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision

to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation or for internal reporting purposes.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete

multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUB INSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to

keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for twenty-five (25) years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with

applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. PRINCIPAL INSTITUTION and SUB INSTITUTION shall each at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination

of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Neil White C/O Tina Samuel
Clinical Research Coordinator
Department of Surgery, Cumming School of Medicine
#310625, 3rd Floor, South Health Campus, 4448 Front St. S.E., Calgary, AB T3M 1M4
Phone: 403-956-3687 or 403-617-3313
E-mail: tina.samuel@ahs.ca or tina.samuel2@ucalgary.ca

to the SUB INSTITUTION:

Alberta Health Services
Legal & Privacy
10301 Southport Lane SW
Calgary, Alberta, Canada T2W 1S7
Attn: Mark Maxwell, Legal Counsel
Tel: (403) 210-6950

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ June 7, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ JUN 05 2019

Marcello Tonelli — Date

Senior Associate Dean, Clinical Research

SUB INVESTIGATOR:

Dr. Neil White

Signature: _____ June 10th, 2019

Date

SUB INSTITUTION:

ALBERTA HEALTH SERVICES

Authorized Signatures: _____ June 5, 2019

Becky Wong — Date

Director, Health System Access

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2019-	1815.00	722.37	180.00	0	30.00	0	2,640.00	0	
June 30, 2019-	6,800.00	2706.4	720.00	0	130.00	0	300.00	0	
September 30, 2019-	8,550.00	3402.9	1,000.00	0	200.00	0	300.00	0	
December 30, 2019-	9,155.00	3643.69	1,060.00	0	210.00	0	330.00	0	
TOTAL	26,320.00	10,475.36	2,960.00	0.00	570.00	0.00	3,570.00	0.00	43,895.36

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2020-	10,155.00	7006.95	1220.00	0.00	250.00	0.00	1380.00	0.00	
June 30, 2020-	11,300.00	7797	1,440.00	0.00	310.00	0.00	300.00	0.00	
September 30, 2020-	11,050.00	4397.9	1,400.00	0.00	300.00	0.00	300.00	0.00	
December 30, 2020-	11,300.00	4497.4	1,440.00	0.00	310.00	0.00	300.00	0.00	
TOTAL	21,455.00	23,699.25	5,500.00	0.00	1,170.00	0.00	2,280.00	0.00	54,104.25

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (39.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2021-	5,250.00	2089.5	840.00	0.00	210.00	0.00	1050.00	0.00	
June 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	0.00	0.00	
September 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	0.00	0.00	
December 30, 2021-	2,500.00	995	400.00	0.00	100.00	0.00	1,500.00	0.00	
TOTAL	12,750.00	5,074.50	2,040.00	0.00	510.00	0.00	2,550.00	0.00	22,924.50

TOTAL BUDGET: $120,924.11 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

120,924.11

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q1	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q2	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 3 participants x $250/participant =	$750
			C$6,800
	Q3	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
			C$8,550
	Q4	Enrollment - 11 participants x $605/participant =	$6,655
		12 weeks – 10 participants x $250/participant =	$2,500
			C$9,155
Year 2020:	Q1	Enrollment - 11 participants x $605/participant =	$6,655
		12 weeks – 11 participants x $250/participant =	$2,750
		52 weeks – 3 participants x $250/participant =	$750
			C$10,155
	Q2	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 11 participants x $250/participant =	$2,750
		52 weeks – 10 participants x $250/participant =	$2,500
			C$11,300
	Q3	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 10 participants x $250/participant =	$2,500
			C$11,050
	Q4	Enrollment - 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 11 participants x $250/participant =	$2,750
			C$11,300
Year 2021:	Q1	12 weeks - 10 participants x $250/participant =	$2,500
		52 weeks – 11 participants x $250/participant =	$2,750
			C$5,250
	Q2	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q3	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q4	52 weeks – 10 participants x $250/participant =	$2,500

C$2,500

Participant Parking:

Year 2019:	Q1	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q2	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 3 participants x $40/participant =	$120
			C$720
	Q3	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
			C$1,000
	Q4	Enrollment - 11 participants x $60/participant =	$660
		12 weeks – 10 participants x $40/participant =	$400
			C$1,060
Year 2020:	Q1	Enrollment - 11 participants x $60/participant =	$660
		12 weeks – 11 participants x $40/participant =	$440
		52 weeks – 3 participants x $40/participant =	$120
			C$1,220
	Q2	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 11 participants x $40/participant =	$440
		52 weeks – 10 participants x $40/participant =	$400
			C$1,440
	Q3	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 10 participants x $40/participant =	$400
			C$1,400
	Q4	Enrollment - 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 11 participants x $40/participant =	$440
			C$1,440
Year 2021:	Q1	12 weeks - 10 participants x $40/participant =	$400
		52 weeks – 11 participants x $40/participant =	$440
			C$840
	Q2	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q3	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q4	52 weeks – 10 participants x $40/participant =	$400
			C$400

Participant Beverage/Food card:

Year 2019:	Q1	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q2	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 3 participants x $10/participant =	$30
			C$130
	Q3	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
			C$200

	Q4	Enrollment - 11 participants x $10/participant =	$110
		12 weeks – 10 participants x $10/participant =	$100
			C$210
Year 2020:	Q1	Enrollment - 11 participants x $10/participant =	$110
		12 weeks – 11 participants x $10/participant =	$110
		52 weeks – 3 participants x $10/participant =	$30
			C$250
	Q2	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 11 participants x $10/participant =	$110
		52 weeks – 10 participants x $10/participant =	$100
			C$310
	Q3	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 10 participants x $10/participant =	$100
			C$300
	Q4	Enrollment - 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 11 participants x $10/participant =	$110
			C$310
Year 2021:	Q1	12 weeks - 10 participants x $10/participant =	$100
		52 weeks – 11 participants x $10/participant =	$110
			C$210
	Q2	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q3	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q4	52 weeks – 10 participants x $10/participant =	$100
			C$100

Investigational Drug Service

Year 2019:	Q1	Start Up Fee =	$1,500
		Maintenance Fee - =	$1,050
		Dispensing fee – 3 participants x $30/participant =	$90
			C$2,640
	Q2	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q3	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q4	Dispensing fee – 11 participants x $30/participant =	$330
			C$330
Year 2020:	Q1	Maintenance Fee - =	$1,050
		Dispensing fee – 11 participants x $30/participant =	$330
			C$1,380
	Q2	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q3	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
	Q4	Dispensing fee – 10 participants x $30/participant =	$300
			C$300
Year 2021:	Q1	Maintenance Fee - =	$1.050
			C$1,050

Q2	Maintenance Fee -	=	$0 C$0
Q3	Maintenance Fee -	=	$0 C$0
Q4	Close-out Fee	=	$1,500 C$1,500

H. INDIRECT COSTS

1. General & Administrative:

The rate at the South Health Campus is the University of Calgary rate, 39.8%. All salaries and wages, and fringe benefits are included in the calculation. The participant support costs such as parking and beverage/food cards, and the Investigational Drug Services, are not included.

SUB-SITE AGREEMENT

This Sub-Site Agreement ("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. Aaron Nauth

Unity Health Toronto

800-55 Queen Street EastToronto, Ontario M5C 1R6 (the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Unity Health Toronto at its St. Michael's site

30 Bond Street

Toronto, Ontario M5B 1W8

(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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The Parties hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement and the Protocol. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The Parties will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws , guidelines and regulations including but not limited to the Canada Food and Drugs Act and all regulations made pursuant thereto, Health Canada's Therapeutic Products Directorate Guidelines and regulations, the Declaration of Helsinki and the ICH

Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: "Ethical Conduct of Research Involving Humans", published December 2014 as amendment from time to time..

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INSTITUTION shall obtain and maintain all applicable government and/or regulatory approvals for the Clinical Study in Canada and shall forward such approvals to the SUB INSTITUTION and SUB INVESTIGATOR prior to initiation of the Clinical Study;

(ii) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws. Notwithstanding the foregoing, patient medical records are and shall at all times remain the property of the SUB INSTITUTION and any access to same by PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION shall be for audit, monitoring and verification purposes only and does not imply a right to copy same, save and except in accordance with the patient informed consent and applicable Privacy Laws (defined below). In accessing the Data, the Parties shall (a) comply with applicable health information and privacy legislation including, the Personal Information Protection and Electronic Documents Act, S.C. 2000, c. 5 (PIPEDA) and Ontario's Personal Health Information Protection Act (PHIPA) (collectively, "Privacy Laws"); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any

Clinical Study subject's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Clinical Study subject ("SUBJECT"); (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of any SUBJECT to be readily ascertained; (e) not make any attempt to contact any SUBJECT to obtain additional Health Information unless the SUBJECT has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with this clause by these persons; and (g) ensure that if the identity of any SUBJECT is disclosed to PRINCIPAL INSTITUTION or its employees, agents, or consultants, such information shall not be disclosed to any third parties, except where such disclosure is required by law.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, provided that such copies do not include Health Information, including but not limited to SUBJECT medical records ,and shall produce such documents (or copies thereof) to such regulatory authority when required, if legally permissible. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION promptly, if legally permissible, upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities if legally permissible

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the study drug Ketotifen 2 ("Study Drug") and placebo to the SUB INSTITUTION and SUB INVESTIGATOR in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide in writing all relevant published information on all drugs being used in the conduct of the Clinical Study, including, without limitation, the Study Drug and placebo and all other information necessary and sufficient to obtain informed consent from all potential Participants and approval from the REB and any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION and SUB INVESTIGATOR shall comply with any directions or instructions provided by the PRINCIPAL

INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION to the SUB INVESTIGATOR shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return any or all of the unused Study Drug Study. Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: Unity Health Toronto

Address of Payee: co/ Aaron Nauth/Milena Vicente

800-55 Queen Street East, Toronto, Ontario Canada M5C 1R6

2.3 Invoices shall be:

(i) Billed to: The University of Calgary

2500 University Drive NW

Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation.

(c) Notwithstanding anything in this Agreement to the contrary and without further notice, the Parties hereto acknowledge and agree that each of the Parties may disclose the existence of this Agreement, the title of the Protocol, identify the Parties to this Agreement, and disclose the amount of funding actually received from the PRINCIPAL INSTITUTION pursuant to this Agreement, including but not limited to acknowledgement in the SUB INSTITUTION's annual report or in any publication or presentation relating to the results of the Clinical Study as provided herein; and that the SUB INVESTIGATOR or any Co-Investigators may disclose the same information in a curriculum vitae.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or

presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete from such Proposed Publication, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, (as defined below), excluding data/results or Clinical Study methods sufficient for the requirements of an academic journal. Other than with respect to Confidential Information, nothing herein shall be construed as granting editing rights of the Proposed Publication to PRINCIPAL INSTITUTION and/or PRINCIPAL INVESTIGATOR. The final analysis and interpretation of the data generated at SUB INSTITUTION in the performance of this Clinical Study remains with the SUB INVESTIGATOR. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. Authorship and other matters relating to publications shall be determined in accordance with International Committee of medical journal Editors ("ICMJE") guidelines. The SUB INVESTIGATOR and/or SUB INSTITUTION shall have right to name PRINCIPAL INSTITUTION as the funding source and PRINCIPAL INSTITUTION in all publications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUBINSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature

(collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to Confidential Information: (a) that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) received by a party to this Agreement from any third party not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) that must be reasonably disclosed to potential SUBJECTS during the recruitment process, and subjects who are or were enrolled in the Clinical Study, or any of their lawful representatives, in order to obtain and maintain information that is required to answer a patient's reasonable questions during the informed consent process; (g) that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement. PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION hereby grants to the SUB INVESTIGATOR and the SUB INSTITUTION a non-exclusive, royalty-free license to use data generated by this Clinical Study for their own academic, clinical, administrative and research purposes and for publication in accordance with Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION for purposes of observing compliance with this Agreement, and excepting all medical records reasonably

required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and Privacy Laws, relating to the use, protection, disclosure, return or disposal of Health Information; (b) use Health Information only for the purpose of conducting the Clinical Study in accordance with the informed consent; (c) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (d) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (e) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law; (f) dispose of Health Information in accordance with the terms of the Protocol and any other written instructions from the disclosing party related to retention and disposal of Health Information; and (g) use appropriate security safeguards to protect Health Information from unauthorized access or use.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

7.3 PRINCIPAL INSTITUTION and PRINCIPAL INVESTIGATOR hereby grant to the SUB INSTITUTION and SUB INVESTIGATOR a non-exclusive, royalty-free license to use all IP created by the SUB INSTITUTION or SUB INVESTIGATOR during the performance of the Clinical Study for their own academic, clinical,

administrative and research purposes and for publication in accordance with Section 4 of this Agreement

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. Each Party shall at its sole cost and expense, procure and maintain insurance policies sufficient to cover their obligations set forth in this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION and SUB INSTITUTION shall at their sole cost and expense, procure and maintain insurance policies or self-insurance of general liability insurance with limits of not less than $5,000,000.00 per occurrence, and $5,000,000.00 annual aggregate. The minimum amounts of insurance coverage required shall not be construed to create a limit of either Party's liability with respect to its indemnification obligations under this Agreement. The PRINCIPAL INSTITUTION and SUB INSTITUTION each shall provide the other Parties with written evidence of such insurance upon request from the other. Additionally, a Party shall provide the other Parties with written notice thirty (30) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 In the agreement between the PRINCIPAL INSTITUTION Bay Area Research Logistics ("BARL") (the manufacturer of the Study Drug), BARL committed to the following:

BARL will perform all packaging and logistical operations in accordance with GMP standards. An appropriate level of QA and QC checks will be determined and implemented. BARL will prepare all relevant documentation. BARL shall indemnify and hold harmless the Sponsor and any institutions participating in the Study for any third party claims arising from the negligence or willful misconduct of BARL in respect of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in material breach of any of the terms of this Agreement and if thirty (30) days after written notice of material breach has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If the Protocol is not approved by the REB, or if the Clinical Study is suspended or approval is withdrawn by the REB and/or regulatory authorities, the SUB INSTITUTION may terminate this Agreement immediately.

9.4 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may immediately suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.5 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.6 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.7 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.8 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.9 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.10 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

9.11 In the event of early termination of this Agreement or completion of the Clinical Study, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in Attachment B for all completed services related to the Clinical Study up to the effective date of termination of this Agreement. All outstanding invoices shall be submitted to the PRINCIPAL INSTITUTION within thirty (30) days of completion of the Clinical Study or effective date of termination of this Agreement.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Aaron Nauth
Unity Health Toronto
800-55 Queen Street EastToronto, Ontario M5C 1R6
Phone: 416-864-6060 ext. 6017

to the SUB INSTITUTION:

Dalton Charters
Senior Director, Research Operations
Unity Health Toronto
30 Bond Street
Toronto, Ontario M5B 1W8
Phone: 416-864-6060 ext. 2558
Fax: 416-864-6043

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Ontario and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

15.3 The Parties agree that, in the event terms of this Agreement and the terms of the Protocol or any other document concerning the Clinical Study conflict, the terms of this Agreement shall govern and apply for legal mattes while the Protocol shall govern for scientific or clinical care purposes.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Force Majeure

No Party shall be responsible to the others for any delay in the performance of, or failure to perform, this Agreement where such delay or failure is caused by circumstances beyond the reasonable control of the affected Party including, without limitation, strikes, lockouts or any other labour disruptions, war, civil commotion, natural disaster, disease or epidemics, or acts of God. In the event of any such delay or failure in performance, the affected Party shall be granted an extension of time for performance that is equitable in light of the cause of the delay.

20. Survival

The terms and of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, 16 and 20.

21. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ 09/Sept/19

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ 29/AUG/19

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____ 29-July-2019

Dr. Aaron Nauth — Date

SUB INSTITUTION:

UNITY HEALTH TORONTO

Authorized

Signatures: _____ 25/8/019

Dr. Ori Rotstein Date

Vice President, Research & Innovation

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT A -
Prime Funding.pdf

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

ATTACHMENT C - St
Michael's Site 10 Budg

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. Thomas Goetz

208-1160 Burrard Street, Vancouver, British Columbia, Canada, V6Z 2E8

(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

The University of British Columbia

103 – 6190 Agronomy Road, Vancouver, British Columbia, V6T 1Z3 ("UBC")

-and-

OF THE FOURTH PART

Providence Health Care Society

400 – 1190 Hornby Street, Vancouver, British Columbia, Canada V6Z 2K5

OF THE FIFTH PART

(UBC and PHCS together the "SUB INSTITUTION")

(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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans. For greater certainty, the use of placebo in connection with the Project will not constitute a violation of the terms of this Agreement.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall, on reasonable notice and during regular business hours, permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required and lawfully authorized. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the drug ("Study Drug") and placebo ("Placebo"), as described in the Protocol, in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be only administered to Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: The University of British Columbia

Address of Payee: The University of British Columbia
Contracts Officer, UILO
103 – 6190 Agronomy Road
Vancouver, British Columbia
Canada V6T 1Z3 Re: UBC File: F18-02842

2.3 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose the existence of the Agreement, the Parties to the Agreement, the amount of funding received by the SUB INSTITUTION from the PRINCIPAL INVESTIGATOR and the title of the Study in annual reports

or in any publication or presentation relating to the results of the Study, or to the extent as required by law, Court order, or regulation.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUBINSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is designated as "confidential" (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are

subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; (h) information that is reasonably required for the medical treatment or counseling of Participants, or (i) information that is published in accordance with Section 4 of this Agreement.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be first disclosed by the SUB INSTITUTION AND SUB INVESTIGATOR except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement. For greater certainty, Clinical Study Data will no longer be considered the Confidential Information of the PRINCIPAL INVESTIGATOR once it falls into one or more of the exceptions to Confidential Information set out in Section 5.1.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, which may include, without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta) and the *Freedom of Information and Protection of Privacy Act* (British Columbia); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR

(together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, , formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study ("Study IP") is the sole and exclusive property of the PRINCIPAL INSTITUTION. The PRINCIPAL INSTITUTION hereby grants to the SUB INSTITUTION and SUB INVESTIGATOR a non-exclusive, royalty-free, irrevocable, perpetual right to use any and all Study IP for the purpose of the Study and internal and academic research purposes.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. Each Party shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate to cover its obligations hereunder. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties.

8.4 The PRINCIPAL INSTITUTION has entered into an agreement with Bay Area Research Logistics ("BARL") in order to procure the Clinical Study drug and placebo. The PRINCIPAL INSTITUTION's represents and warrants that its agreement with BARL provides as follows:

BARL will perform all packaging and logistical operations in accordance with GMP standards. An appropriate level of QA and QC checks will be determined and implemented. BARL will prepare all relevant documentation. BARL shall indemnify and hold harmless the Sponsor and any institutions participating in the Study for any third party claims arising from the negligence or willful misconduct of BARL in respect of the scope of work contained within this Agreement.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Thomas Goetz
208-1160 Burrard Street
Vancouver, British Columbia
Canada V6Z 2E8

to the SUB INSTITUTION:

If to UBC
Contracts Officer
UBC File No. F18-02842
The University of British Columbia
University-Industry Liaison Office
#103 - 6190 Agronomy Road
Vancouver, British Columbia
Canada V6T 1Z3
Tel: (604) 822-0892
Fax: (604) 822-8589

If to PHCS

Providence Health Care Society
Dr. Darryl Knight, MD
Vice President, Research & Academic Affairs
President, Providence Health Care Research Institute

Suite 400 – 1190 Hornby Street
Vancouver, British Columbia
Canada V6Z 2K5
Tel: (604) 806-9608
Fax: (604) 806-8568

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

The Parties agree to remain silent.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ September 23, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ SEP 2 3 2019

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____ September 17, 2019

Date

SUB INSTITUTION:

THE UNIVERSITY OF BRITISH COLUMBIA

LEGAL APPROVED TH

Authorized Signatures: _____ Mario Kasapi 2019.08.02 08:05:05 -07'00'

Date

PROVIDENCE HEALTH CARE SOCIETY

Per: _____ Digitally signed by Dr. Darryl Knight DN: cn=Dr. Darryl Knight, o, ou=VP, Research and Academic Affairs, PHC and Associate Dean, Research, Faculty of Medicine, UBC, email=dknight2@providencehealth.bc.ca, c=CA Date: 2019.09.18 10:33:41 -07'00' September 18th, 2019

Dr. Darryl Knight — Date

Vice President, Research & Academic Affairs

President, Providence Health Care Research Institute

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

AWARD/CONTRACT	1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 700)	RATING	PAGE OF PAGES 1 | 17
2. CONTRACT (Proc. Inst. Ident.) NO. W81XWH-17-1-0665	3. EFFECTIVE DATE 30 Sep 2017	4. REQUISITION/PURCHASE REQUEST/PROJECT NO. 0011000131	

5. ISSUED BY	CODE W81XWH	6. ADMINISTERED BY (If other than Item 5)	CODE
USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST FORT DETRICK MD 21702-5014		See Item 5	

7. NAME AND ADDRESS OF CONTRACTOR (No., street, city, county, state and zip code) GOVERNORS OF THE UNIVERSITY OF CALGARY, 2500 UNIVERSITY DR NW CALGARY T2N 1N4	8. DELIVERY [ ] FOB ORIGIN [X] OTHER (See below) 9. DISCOUNT FOR PROMPT PAYMENT Net 30 Days 10. SUBMIT INVOICES 1 (4 copies unless otherwise specified) TO THE ADDRESS SHOWN IN: ITEM
CODE 1C344 FACILITY CODE	

11. SHIP TO/MARK FOR	CODE W81ZSQ	12. PAYMENT WILL BE MADE BY	CODE HQ0400
FORT DETRICK- CDMRP FORT DETRICK- CDMRP 1120 FORT DETRICK FREDERICK MD 21702		DEFENSE FINANCE AND ACCOUNTING SERVICE DFAS-INDY VP GFEDS 8899 E 56TH STREET INDIANAPOLIS IN 46249-3800	

13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION: [ ] 10 U.S.C. 2304(c)( ) [ ] 41 U.S.C. 253(c)( )	14. ACCOUNTING AND APPROPRIATION DATA See Schedule

15A. ITEM NO.	15B. SUPPLIES/ SERVICES	15C. QUANTITY	15D. UNIT	15E. UNIT PRICE	15F. AMOUNT
	SEE SCHEDULE				
				15G. TOTAL AMOUNT OF CONTRACT	$2,440,796.00

16. TABLE OF CONTENTS

(X)	SEC.	DESCRIPTION	PAGE(S)	(X)	SEC.	DESCRIPTION	PAGE(S)
		PART I - THE SCHEDULE				PART II - CONTRACT CLAUSES	
X	A	SOLICITATION/ CONTRACT FORM	1		I	CONTRACT CLAUSES	
	B	SUPPLIES OR SERVICES AND PRICES/ COSTS				PART III - LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACH.	
	C	DESCRIPTION/ SPECS./ WORK STATEMENT			J	LIST OF ATTACHMENTS	
	D	PACKAGING AND MARKING				PART IV - REPRESENTATIONS AND INSTRUCTIONS	
	E	INSPECTION AND ACCEPTANCE			K	REPRESENTATIONS, CERTIFICATIONS AND OTHER STATEMENTS OF OFFERORS	
	F	DELIVERIES OR PERFORMANCE			L	INSTRS., CONDS., AND NOTICES TO OFFERORS	
	G	CONTRACT ADMINISTRATION DATA			M	EVALUATION FACTORS FOR AWARD	
	H	SPECIAL CONTRACT REQUIREMENTS					

CONTRACTING OFFICER WILL COMPLETE ITEM 17 (SEALED-BID OR NEGOTIATED PROCUREMENT) OR 18 (SEALED-BID PROCUREMENT) AS APPLICABLE

17. [ ] CONTRACTOR'S NEGOTIATED AGREEMENT Contractor is required to sign this document and return copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)

18. [X] SEALED-BID AWARD (Contractor is not required to sign this document.) Your bid on Solicitation Number _____ REF: Sol 60800 Award Specific T & C including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the terms listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your bid, and (b) this award/contract. No further contractual document is necessary. (Block 18 should be checked only when awarding a sealed-bid contract)

19A. NAME AND TITLE OF SIGNER (Type or print) Lorna Very / Director, Grants, Awards & Ethics	20A. NAME OF CONTRACTING OFFICER TERESA PARKER-REESER / GRANTS OFFICER TEL: 301-619-2171 EMAIL: Teresa.H.ParkerReeser.civ@mail.mil	
19B. NAME OF CONTRACTOR BY _____ (Signature of person authorized to sign)	19C. DATE SIGNED Oct 24 2017	20B. UNITED STATES OF AMERICA BY _____ (Signature of Contracting Officer)
		20C. DATE SIGNED 24-Sep-2017

AUTHORIZED FOR LOCAL REPRODUCTION
Previous edition is NOT usable

STANDARD FORM 26 (REV. 5/2011)
Prescribed by GSA – FAR (48 CFR) 53.214(a)

Section 00010 - Solicitation Contract Form

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
0001					$2,440,796.00
	Grant - OR160026 COST Peer Reviewed Orthopedic Research Program Clinical Translational Research Award				
	FOB: Destination				
				ESTIMATED COST	$2,440,796.00

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
000101					$0.00
	FY16 OR160026 Funding COST Peer Reviewed Orthopedic Research Program Clinical Translational Research Award FOB: Destination PURCHASE REQUEST NUMBER: 0011096131				
				ESTIMATED COST	$0.00
	ACRN AA CIN: GFEBS001109613100001				$1,459,924.16

ITEM NO	SUPPLIES/SERVICES	QUANTITY	UNIT	UNIT PRICE	AMOUNT
000102					$0.00
	FY17 OR160026 Funding COST Peer Reviewed Orthopedic Research Program Clinical Translational Research Award FOB: Destination PURCHASE REQUEST NUMBER: 0011096131				
				ESTIMATED COST	$0.00
	ACRN AB CIN: GFEBS001109613100002				$980,871.84

DELIVERY INFORMATION

CLIN	DELIVERY DATE	QUANTITY	SHIP TO ADDRESS	DODAAC
0001	POP 30-SEP-2017 TO 29-SEP-2021	N/A	FORT DETRICK - CDMRP FORT DETRICK - CDMRP 1120 FORT DETRICK FREDERICK MD 21702 FOB: Destination	W91ZSQ
000101	POP 30-SEP-2017 TO 29-SEP-2021	N/A	N/A FOB: Destination	
000102	POP 30-SEP-2017 TO 29-SEP-2021	N/A	N/A FOB: Destination	

ACCOUNTING AND APPROPRIATION DATA

AA: 0972016201701300001831033333741O R.0002688.6.1 6100.9000021001
COST CODE: A7444
AMOUNT: $1,459,924.16
CIN GFEBS001109613100001: $1,459,924.16

AB: 0972017201801300001831033333741O R.0002688.7.1 6100.9000021001
COST CODE: A7444
AMOUNT: $980,871.84
CIN GFEBS001109613100002: $980,871.84

CLAUSES INCORPORATED BY FULL TEXT

U.S. ARMY MEDICAL RESEARCH ACQUISITION ACTIVITY AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS WITH INSTITUTIONS OF HIGHER EDUCATION, HOSPITALS, AND NON-PROFIT ORGANIZATIONS

DIVISION I – AWARD COVER PAGES

Principal Investigator Dr. Kevin Hildebrand

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

Technical Abstract

Background:
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. Post-traumatic joint contractures, or loss of motion after injury, are a debilitating condition following elbow trauma. Limited elbow motion interferes with feeding, dressing, grooming, and reaching for objects, which markedly reduces the quality of life. Many affected individuals are in the 20 – 60 year age group and thus elbow contractures limit productivity in civilian and military populations. Our laboratory research on post-traumatic joint contractures over the last 18 years has implicated a myofibroblast-mast cell-neuropeptide axis of fibrosis in the joint capsule, the critical structure limiting joint motion. We have demonstrated in a rabbit model of posttraumatic contractures that ketotifen, a mast cell stabilizer that prevents growth factor release, decreased contracture severity by 50% concomitant with decreased numbers of myofibroblasts, mast cells, neuropeptide containing nerve fibres, and mensures of fibrosis in the joint capsule. These results are very exciting because ketotifen is the first and only agent demonstrated to significantly decrease contracture severity that also has a wide safety profile, has been used in the chronic treatment of asthma for over 40 years in humans, is available as an oral preparation, and is low cost. Recent advances have positioned us to apply for the FY16 PRORP CTA. These include experiments revealing a dose-response effect of ketotifen for joint contracture severity inhibition in the preclinical model of post-traumatic contractures, completion of the recruitment phase for an randomized clinical trial (RCT) comparing one dose of ketotifen (5 mg twice daily) administered over 6 weeks to a lactose placebo for the prevention of post-traumatic elbow contractures (ClinicalTrials.gov Identifier NCT01902017), and the implementation of a CTDA from the FY14 PRORP funding cycle (eBRAP Log No OR140142) with the purpose to develop the infrastructure to conduct a multicenter Phase III randomized, double-blind, placebocontrolled

clinical trial to compare multiple doses of ketotifen to a lactose placebo. These three advances highlight the clinical trial expertise in Calgary, the need to consider a dosing effect for ketotifen, and the establishment of the infrastructure for a multicenter clinical trial.
Research Hypothesis: Ketotifen is superior to a lactose placebo in reducing joint contracture severity in adult participants with isolated elbow fractures or dislocations.
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.
Trial Design: A Phase III randomized, controlled, double blinded multicenter trial with 3 parallel groups (ketotifen 2 mg or 5 mg or lactose placebo twice daily for 6 weeks) and a primary endpoint of elbow extensionflexion range of motion (ROM) arc at 12 weeks post-randomization. Eligibility: age $\geq$ 18 years old; isolated distal humerus and/or proximal ulna and/or proximal radius fractures and/or elbow dislocations requiring an operation; injury $\leq$ 7 days; able to mobilize elbow within 2 weeks of injury, no previous elbow contracture or arthritis. Outcome Measures: ROM; Disability Arm, Shoulder, Hand; Oxford Elbow Score; radiographs; reoperation 2 – 52 weeks post-randomization.
Military Benefit and Clinical Impact:
A recent review of extremity injuries in war by the US military has highlighted joint stiffness and contractures as a major complication that limits function. Injuries to Service members also occur in training exercises. Ketotifen has a long history of human clinical use with an oral route of administration, wide safety profile, and low cost. It is the only pharmaceutical possibility available in the foreseeable future. Easy transportability of ketotifen has military relevance. Service members can be returned to full-duty status either sooner than is typical, or Service members and Veteranss can enjoy a higher quality of life, following elbow injuries. A related potential use for ketotifen is after surgical release of post-traumatic elbow contractures to enhance the improvement in motion after the procedure. Joint contractures complicate other extremity injuries and the results of this trial would be relevant in these cases. Another procedure where contractures are a postoperative complication is total knee arthroplasty, which is commonly performed in civilian and Veterans populations. Adjuncts to operative reversal of contractures following knee replacements could be an indication for ketotifen. In addition to developing a translational, scientifically sound therapy for joint fibrosis and contracture through repurposing an established drug for a new indication, our findings might stimulate research in other conditions characterized by fibrosis that affects the lung, kidney, heart, liver, and skin.

Recipient's Business Official

Authorized Official: Dallas Callaway
Title: Research Grants Officer
Phone: 403-210-9815
Email: dacallaw@ucalgary.ca
DUNS Number: 207663915

Grants Administration Office

Grants Specialist: Kenneth Grenier
Phone: 301-619-2728
Email: kenneth.e.grenier2.civ@mail.mil

Grants Officer's Representative

Congressionally Directed Medical Research Program Office
Phone: 301-619-7071
Email: usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil

Applicability

These award specific research terms and conditions are applicable to assistance agreement awards (grants and cooperative agreements) issued by the US Army Medical Research Acquisition Activity (USAMRAA) made with institutions of higher education, hospitals, and other non-profit organizations.

Authorities

This new award is a grant made under the authority of 10 U.S.C. 2358.

This award is governed by the guidance in 2 Code of Federal Regulations (CFR) part 200, "Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards," as modified and supplemented by the Department of Defense's (DoD) interim implementation found at 2 CFR part 1103, "Interim Grants and Cooperative Agreements Implementation of Guidance in 2 CFR part 200" (79 FR 76047, December 19, 2014), all of which are incorporated herein by reference.*

Provisions of Chapter I, Subchapter C of Title 32, CFR, "DoD Grant and Agreement Regulations," parts 26, 28, 34, 37, and 1125 continue to be in effect and are incorporated herein by reference, with applicability as stated in those provisions.

For nonprofit organizations identified in Appendix VIII to 2 CFR part 200, "Nonprofit Organizations Exempted From Subpart E– Cost Principles," and for subawards to commercial organizations, the cost principles in part 31 of Chapter 1 of Title 48, CFR, "Federal Acquisition Regulation" (FAR), and part 231 of Chapter 2 of Title 48, "DoD FAR Supplement," are incorporated herein by reference, with applicability as stated in those provisions.

*Note that OMB amended 2 CFR 200.110(a) on September 10, 2015, to permit recipients to continue to comply with the procurement standards in previously applicable OMB guidance, rather than the procurement standards in 2 CFR 200.317-200.326, through the end of the two recipient fiscal years that begin on or after December 26, 2014. DoD implemented those previous procurement standards in DoDGARs part 32 (32 CFR part 32) for institutions of higher education, hospitals and other nonprofit organizations and in DoDGARs part 33 (32 CFR part 33) for States and local and Indian tribal governments. If you choose to use those previous procurement standards, rather than the standards in PROC Articles I and II of the DoD R&D General T&Cs, you must document that decision in your internal procurement policies.

Copies of the above can be obtained from:

Office of Management and Budget
EOP Publications Office
New Executive Office Building
725 17th Street, NW, Room 2200
Washington, DC 20503
Telephone: (202) 395-7332
Website: http://www.whitehouse.gov/omb/

Terms and Conditions Incorporated by Reference

The following terms and conditions are incorporated herein by reference:

a. Division III - USAMRAA General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations (effective February 2017), available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3.

b. The DoD R&D General Terms and Conditions (July 2016), available at http://www.onr.navy.mil/Contracts-Grants/submit-proposal/grants-proposal/grants-terms-conditions.aspx.

These USAMRAA Award Specific Research Terms and Conditions are in addition to the terms and conditions incorporated above.

Order of Precedence

Any inconsistencies in the requirements of this award will be resolved in the following order:

a. Federal statutes
b. Federal regulations
c. 2 CFR part 200 with amendments, as modified and supplemented by DoD's interim implementation found in 2 CFR part 1103
d. Division II - USAMRAA Award Specific Research Terms and Conditions
e. Division III - USAMRAA General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations (effective February 2017)
f. DoD R&D General Terms and Conditions (July 2016)

Acceptance of Award

You are not required to countersign this award. In case of disagreement with any requirements in this award, contact the USAMRAA Grants Officer in order to resolve the issue(s). Do not assess any costs to the award or accept any payments until the issue(s) is resolved. Note, however, that initiating performance under this award constitutes acceptance of this award, including the terms and conditions.

Catalog of Federal Domestic Assistance Number: 12.420 - Military Medical Research and Development

Statement of Work and Budget

The revised Statement of Work (SOW) date 31 July 2017 and the revised budget dated 18 September 2017 for your application submitted in response to the Fiscal Year 2016 DoD Peer Reviewed Orthopedic Research Program Announcement (Funding Opportunity Announcement Number W81XWH-16-PRORP-CTA, which closed 7 December 2016) are incorporated herein by reference.

Recipient's Indirect Cost Rate at the Start of the Performance Period: 39.8%

Funding Overview

	Federal funds	Cost Sharing	Total amount
Obligated or deobligated this action	$2,440,796	N/A	$2,440,796
Cumulative obligations to date, including this and previous actions	$2,440,796	N/A	$2,440,796
Planned project costs in the currently approved budget through the end of the period of performance, to include any future incremental funding obligations	$2,440,796	N/A	$2,440,796
Total value, which includes any unexercised options for which amounts were established in the award	$2,440,796	N/A	$2,440,796

DIVISION II – AWARD SPECIFIC RESEARCH TERMS AND CONDITIONS

TABLE OF CONTENTS

1. Award Type
2. Award Modification
3. Maximum Obligation
4. Expiration of Funds

5. Fixed-Amount Awards and Fixed-Amount Subawards
6. Prior Approval Requirements
7. Title to Property
8. Financial Reporting Requirements
9. Patents and Inventions Reporting Requirements
10. Technical Reporting Requirements
11. Publication, Acknowledgement, and Public Release
12. Payment Requests
13. Electronic Payment Instructions
14. Closeout Requirements
15. Prohibition of Use of Laboratory Animals
16. Prohibition of Use of Human Subjects
17. Prohibition of Use of Cadavers
18. Interim Progress Review
19. Clinical Trial Registry
20. Required Start Date for Proposed Clinical Trial

AWARD SPECIFIC TERMS AND CONDITIONS

1. Award Type

This is a cost-type award in support of basic or applied research. Construction activities under this award are not authorized. (Reference Department of the Army Pamphlet 420-11, dated 18 March 2010, for additional information regarding construction activities.)

2. Award Modification

The only method by which the award may be modified is by a formal, written modification signed by the USAMRAA Grants Officer. No other communications, whether oral or in writing, are valid to change the terms and conditions of this award.

3. Maximum Obligation

The maximum obligation of the Federal Government for support of this award will not exceed the award amount specified in the award cover pages, as modified. This award will not be modified to provide additional funds for such purposes as reimbursement for unrecovered indirect costs resulting from the establishment of final negotiated rates or for increases in salaries, fringe benefits, changes in exchange rates, or other costs. You may rebudget allowable costs in accordance with applicable cost principles and in accordance with the prior approval requirements as stated in this award.

4. Expiration of Funds

(a) Funds obligated on this award are available for use for a limited period based on the fiscal year (FY) of the funds. That time is considered when establishing your period of performance. This award is funded with FY 2016 funds which will expire for use on September 30, 2022 and FY 2017 funds which will expire for use on September 30, 2023. If the final budget period of this award has expiring funds and you do not anticipate expending the total amount by the end of the period of performance, six months before the end of the period of performance contact the Grants Specialist identified in the cover pages of this award.

(b) It is extremely important that you monitor the established milestones, timelines, expenditures and invoicing to make sure the project is on schedule and that you voucher promptly. **If this award has funds that will expire on September 30, 2022, submit the final SF270 at least 30 days before September 30, 2022 in order to allow sufficient time to process and pay the voucher. If this award has funds that will expire on September 30, 2023, submit the final SF270 at least 30 days before September 30, 2023 in order to allow sufficient time to**

process and pay the voucher. If you have not submitted a final SF270 and been paid before the expiration date of these funds, any excess funds will be deobligated from the award at that time.

5. Fixed-Amount Awards and Fixed-Amount Subawards

You are not authorized to treat this award or any subawards that you enter into under this award, at any tier, as fixed-amount awards. The inherently unpredictable nature of basic and applied research makes it rarely, if ever, possible to define specific research outcomes in advance, which makes fixed-amount awards inappropriate for research. This is not applicable to procurement contracts entered into under this award for acquisition of supplies, equipment, or general support services you need to carry out the project or program.

6. Prior Approval Requirements

You must request prior approval from the USAMRAA Grants Officer for any of the following program or budget revisions:

a. A change in the scope or objective of the project or program under the award, even if there is no associated budget revision that requires our prior approval.

b. A change in a key person(s) identified in the cover pages of the award.

c. The approved principal investigator's (PI) or project director's disengagement from the project for more than three months, or a 25 percent reduction in his or her time devoted to the project.

d. The inclusion of direct costs that require prior approval in accordance with the applicable cost principles, as identified in FMS Article III of the DoD R&D General Terms and Conditions (July 2016). Note the following requirements and limits:

(1) In accordance with applicable cost principles, you must request prior written approval for the incurrence of special or unusual costs.

(2) The requirement for prior written approval of capital expenditures for equipment that is to be used primarily in carrying out the project or program supported by the award is waived for equipment with a unit cost of $25,000 or less. Capital expenditures for equipment with a unit cost over $25,000 require the USAMRAA Grants Officer's prior approval. Note that equipment acquired under the award and charged as direct project costs must be necessary for the conduct of the research project supported by the award. You are prohibited from acquiring equipment under the award merely for the purpose of using unobligated balances.

e. A subaward to another entity under which it will perform a portion of the substantive project or program under the award if it was not included in the approved budget. This does not apply to your contracts for acquisition of supplies, equipment, or general support services you need to carry out the project or program.

f. The transfer (relocation) of the PI and/or research project to another entity.

g. Reimbursing a DoD Military Treatment Facility (MTF) for costs incurred if the MTF is involved in the award. Reimbursing these costs is generally prohibited and only approved under unusual and extraordinary circumstances.

h. Any change in the cost sharing or matching you provide under the award that is included in the approved budget.

i. The need arises for additional Federal funds to complete the project or program.

7. Title to Property

Property acquired in whole or in part with award funds is considered to be excepted property. As such, title is vested to you without further obligation to the Federal Government. Reference PROP Article IV of the DoD R&D General Terms and Conditions (July 2016).

8. Financial Reporting Requirements

a. You must submit Standard Form (SF) 425, "Federal Financial Report," for reporting on this award. Annual and final reports are required.

b. The Federal Financial Reporting period end dates fall on the end of the calendar year for annual reports (12/31), and the end date of the term of award for the final report. Submit annual reports no later than 90 days after the end of the calendar year. Submit final reports no later than 120 days after the end of the period of performance.

c. Submission Instructions:

(1) All SF425 reports must be submitted electronically through the web site https://www.usamraa.army.mil/pages/sf425. The form and instructions can be obtained on this site.

(2) Do not report multiple awards on one report. Each award must be reported separately on its own SF425.

(3) Do not combine multiple SF425s into one submission. Each form must be saved as a separate PDF and submitted individually.

9. Patents and Inventions Reporting Requirements

a. iEdison and annual reporting. You must electronically file Invention Disclosures and Patent Applications using the Interagency Edison (iEdison) system through the National Institutes of Health (https://s-edison.info.nih.gov/iEdison) within the times specified for reporting. In addition, you must report annually any inventions made during the year (within 30 days of the anniversary date of the award) on a DD Form 882, "Report of Inventions and Subcontracts." If there are no inventions during the year, no annual DD Form 882 is required. The DD Form 882 can be accessed at https://www.usamraa.army.mil.

b. Closeout report. A final DD Form 882 is required, whether or not you are reporting an invention. Submit the report within 120 days of end of the period of performance. List all inventions made during the period of performance or state "none," as applicable. The award will not be closed until you have met all reporting requirements.

c. Submit all DD882 reports electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

10. Technical Reporting Requirements

The following technical progress reports are required under this award:

Quarterly Technical Reports

a. For each year of the award, the PI must submit Quarterly Technical Progress Reports covering research results (positive and negative data) over a three month period (quarter). A reporting quarter begins with the start date of the award and restarts annually from that date for the entire period of performance. A Quarterly Technical Progress Report for the fourth quarter each year is not required, as the Annual Technical Report must incorporate all four quarters of progress.

b. Quarterly reports are the most immediate and direct contact between the PI and the Grants Officer's Representative (GOR). The reports provide the means for keeping the US Army Medical Research and Materiel

Command (USAMRMC) advised of developments and problems as the research effort proceeds. The reports also provide a measure against which funding decisions are made.

c. Prepare all Quarterly reports in accordance with the Quarterly Technical Progress Report format, available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3. Each item of the report format must be completed.

d. Each report must be submitted electronically, within 15 days after the end of each quarter, to the Grants Specialist and the GOR at the e-mail addresses specified in the front pages of this award. Name your file with your award number, followed by Year X Quarter Y Report (example: W81XWH-17-1-0665 Year 1 Quarter 1 Report.) If you have questions, contact the GOR.

e. Special Reports

Quad Charts: The Quad Chart (available on https://www.usamraa.army.mil) must be updated and submitted as an appendix.

Annual/Final Technical Reporting Requirements

a. Annual Reports

(1) Annual reports are required and must be prepared in accordance with the Research Performance Progress Report (RPPR). The RPPR is the uniform format for reporting performance progress on Federally-funded research projects and research-related activities.

(2) Annual reports must provide a complete summary of the research results (positive or negative) to date in direct alignment to the approved Statement of Work (SOW). The importance of the report to decisions relating to continued support of the research cannot be over-emphasized. An annual report must be submitted within 30 calendar days of the anniversary date of the award for the preceding 12 month period. If the award period of performance is extended by the USAMRAA Grants Officer, then an annual report must still be submitted within 30 days of the anniversary date of the award. A final report that describes the entire research effort is due upon completion of the extended performance date.

b. Final Reports. A final report must also be prepared in accordance with the RPPR and must be submitted within 120 calendar days of the end of the period of performance. The report must summarize the entire research effort, citing data in the annual reports and appended publications.

c. Prepare the annual and final reports in accordance with the RPPR format, available at http://www.usamraa.army.mil/index.cfm?ID=12&Type=3. Although there is no page limitation for the reports, each report must be of sufficient length to provide a thorough description of the accomplishments with respect to the approved SOW.

d. Reports, in electronic format (PDF or Word file only), must be submitted to https://ers.amedd.army.mil.

Additional information is available on the Researcher Resources website, available at https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting

e. Special Reports

Quad Charts: The Quad Chart (available on https://www.usamraa.army.mil) must be updated and submitted as an appendix.

11. Publication, Acknowledgement, and Public Release

a. Publication. You are encouraged to publish results of the research, unless classified, in appropriate media. Submit one copy of each paper to the GOR simultaneously with its submission for publication. Forward copies of

all publications resulting from the research to the USAMRAA Grants Officer or Grants Specialist as they become available, even though publication may in fact occur subsequent to the termination date of the award. (See Section C of the DoD R&D General Terms and Conditions for the charging of publication costs incurred after the period of performance.)

b. Acknowledgment. You agree that in the release of information relating to this award such release will include the statements below, as applicable. "Information" includes, but is not limited to, news releases, articles, manuscripts, brochures, advertisements, still and motion pictures, speeches, trade association meetings, and symposia.

(1) "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office" and;

(2) "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Orthopedic Research Program under Award No. W81XWH-17-1-0665. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."

(3) "In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture."

(4) "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules."

(5) "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories."

c. Public release. Prior to release to the public, you must notify the USAMRAA Grants Officer and the GOR of the following: planned news releases, planned publicity, advertising material concerning project work, and planned presentations to scientific meetings. This provision is not intended to restrict dissemination of research information; the purpose is to inform the USAMRMC of planned public release of information on USAMRMC-funded research in order to adequately respond to inquiries and to be alert to the possibility of inadvertent release of information which could be taken out of context.

Failure to include the above statements and adhere to the above regulations, when required, may result in loss of funding and/or termination of this award.

12. Payment Requests

Request for Payments - Fully Funded Award

a. Payments. Payments will be made to you upon receipt of a "grant voucher" (used for both grants and cooperative agreements) submitted through the Wide Area Work Flow (WAWF) e-Business Suite in accordance with the Contract Line Item Number (CLIN) structure set forth in this award.

b. Payment requests can be either advance or reimbursement. Select "advance" or "reimbursement" on the grant voucher in WAWF.

c. In order to conserve administrative resources for both parties, you are encouraged to voucher no more frequently than monthly. Failure to voucher at least quarterly may raise concerns about research progress and the need for continued funding.

d. For any advance payment request, you should (1) submit the request approximately 10 days before you anticipate disbursing the requested amount for program purposes, and (2) you must provide an explanation regarding the need for the advance. Include your explanation in the "initiator" block under "comments" or attach an

explanation under "attachments." Advance payments must be limited to the minimum amount needed to meet your actual, immediate cash requirements for carrying out the purpose of the approved program or project, including direct program or project costs and a proportionate share of any allowable indirect costs. All advances must be approved by the Grants Officer. Grants Officer approval will be through approval of the grant voucher.

e. All payments will be made by Electronic Funds Transfer (EFT) to your institution's financial account listed in the System for Award Management (SAM) (available at https://www.sam.gov). Failure to update SAM ensuring active account status will result in nonpayment.

f. Failure to submit required Technical Reports or Federal Financial Reports (SF425s) may delay payments or result in nonpayment.

g. If you fail to perform, the grant voucher will be rejected.

h. Interest Bearing Account. You must deposit all advance payments into an interest bearing account unless one of the following applies:

1. You are exempted by applicable Treasury-State agreements in accordance with the Cash Management Improvement Act (31 USC 3335).
2. You receive less than $120,000 in Federal awards per year.
3. The best reasonably available interest bearing account would not be expected to earn interest in excess of $500 per year on Federal cash balances.
4. The depository would require an average or minimum balance so high that it would not be feasible within the expected Federal and non-Federal cash resources.

i. Interest over the amount of $500 per year must be remitted annually to the U.S. Department of Health and Human Services, Payment Management System, P.O. Box 6021, Rockville, Maryland 20852. A copy of the transmittal letter stating the amount of interest remitted must be sent electronically to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

NOTE: This award is comprised of a clinical study or trial that requires Human Use approval from the USAMRMC Office of Research Protection (ORP). Grant vouchers may be submitted for payments for the first 12 months of this award. No grant voucher may be submitted thereafter until you provide a copy of the ORP approval notification to the cognizant Grants Specialist at usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

13. Electronic Payment Instructions

a. The Wide Area Work Flow (WAWF) e-Business Suite is the required method to electronically process your requests for payments. Once on the WAWF e-Business Suite web site, select the Invoicing, Receipt, Acceptance, and Property Transfer (iRAPT) button to electronically submit "grant vouchers" (used for both grants and cooperative agreements). You must (i) register to use WAWF at https://wawf.eb.mil and (ii) ensure an electronic business point of contact (POC) is designated in the System for Award Management (SAM) site at https://www.sam.gov within ten (10) calendar days prior to requesting a payment for this award.

b. Questions concerning specific payments should be directed to the Defense Finance and Accounting Service (DFAS), Indianapolis, at 1-888-332-7366. **You can also access payment and receipt information using the "myInvoice" button in WAWF at https://wawf.eb.mil.** The award number or grant voucher number will be required to inquire about the status of the payment.

c. The following codes and information are required to initiate the grant voucher and assure successful flow of WAWF documents.

TYPE OF DOCUMENT: **Grant Voucher** ***(Used for both grants and cooperative agreements)***

CAGE CODE: 1C344

ISSUE BY DODAAC: W81XWH

ADMIN BY DODAAC: W81XWH

INSPECT BY DODAAC: W81XWH

ACCEPT BY DODAAC: W81XWH

SHIP TO DODAAC: W81XWH

LOCAL PROCESSING OFFICE DODDAC: Not Applicable

PAYMENT OFFICE FISCAL STATION CODE: HQ0490

EMAIL POINTS OF CONTACT LISTING:
INSPECTOR: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil
ACCEPTOR: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil
RECEIVING OFFICE POC: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil
GRANT ADMINISTRATOR: Leave Blank
GRANTS OFFICER: Leave Blank
ADDITIONAL CONTACT: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil

14. Closeout Requirements

a. In order to close this award, you must submit the following documents within 120 calendar days of the end of the period of performance:

(1) Final SF425, "Federal Financial Report." Submit to: https://www.usamraa.army.mil/pages/sf425. Form and instructions are available on the web site.

(2) Final Technical Report. Submit to: https://ers.amedd.army.mil. Forms and instructions are available on the web site.

(3) Final DD Form 882, "Report of Inventions and Subcontracts." Submit to: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil. Form is available on web site https://www.usamraa.army.mil).

(4) Property Acquired with Award Funds, if applicable. [Reference PROP Article IV of the DoD R&D General Terms and Conditions (July 2016).]

(a) If title to property (equipment and supplies) is excepted property, there is no further obligation to the Federal Government.

(b) If title to equipment under this award is non-excepted property, you must provide a cumulative listing of nonexpendable personal property acquired with award funds. Submit this on your organization's letterhead. Submit to: usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

(c) If title to supplies under this award is non-excepted property, you must submit a statement that: (i) there is, or is not, a residual inventory of unused supplies exceeding $5,000 in total aggregate value; and (ii) if there is, state whether or not the unused items will be needed on other Federally sponsored projects or programs. Submit this on your organization's letterhead. Submit to usarmy.detrick.medcom-usamraa.mbx.aa4@mail.mil.

b. In the event a final audit has not been performed prior to the closing of this award, the Federal Government retains the right to recover an appropriate amount after fully considering the recommendations on disallowed costs resulting from the final audit.

c. You must promptly refund any unspent balances of funds the DoD Component has advanced or paid that is not authorized to be retained by you. Make check payable to the U.S. Treasury and mail to:

USAMRAA
Attn: MCMR-AAP-C
Federal Award Identification No. W81XWH-17-1-0665
820 Chandler Street
Fort Detrick, Maryland 21702-5014

15. Prohibition of Use of Laboratory Animals

Notwithstanding any other terms and conditions contained in this award or incorporated by reference herein, the recipient is expressly forbidden to use or subcontract for the use of laboratory animals in any manner whatsoever without the express written approval of the USAMRMC, Animal Care and Use Review Office (ACURO). Written authorization to begin research under applicable protocol(s) proposed for this award will be issued in the form of an approval letter from the USAMRMC ACURO to the recipient with a copy to the USAMRAA Grants Officer. Furthermore, modifications to already approved protocols require approval by ACURO prior to implementation. For each fiscal year, the recipient must maintain, and upon request from ACURO, submit animal usage information.

Noncompliance with any of these terms and conditions may result in withholding of funds and/or the termination of the award.

The Animal Care and Use Office requirements can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.acuro.

16. Prohibition of Use of Human Subjects

Research under this award involving the use of human subjects, to include research involving the secondary use of human biospecimens and/or human data, cannot begin until the USAMRMC's Office of Research Protections (ORP) provides authorization that the research may proceed. The USAMRMC ORP will issue written approval to begin research under separate notification to you. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct research involving human subjects.

The USAMRMC ORP 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 USAMRMC 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.

The recipient is required to adhere to the following reporting requirements:

Submission of substantive modifications to the protocol, continuing review documentation, and the final report as outlined in the USAMRMC ORP approval memorandum.

Unanticipated problems involving risks to subjects or others, subject deaths related to participation in the research, clinical holds (voluntary or involuntary), and suspension or termination of this research by the IRB, the institution, the Sponsor, or regulatory agencies, must be promptly reported to the USAMRMC ORP.

Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO.

The knowledge of any pending compliance inspection/visits by the FDA, ORP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies, and any instances of serious or continuing noncompliance with regulatory requirements that relate to this clinical investigation or research, must be reported immediately to the USAMRMC ORP.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

DoD requirements for human subjects research, including 32 CFR Part 219, DoD Instruction 3216.02, and USAMRMC ORP Human Research Protection Office submission instructions can be accessed at https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.hrpo.

17. Prohibition of Use of Human Cadavers

Research, development, testing and evaluation (RDT&E), education or training activities involving human cadaveric specimens under this award shall not begin until approval is granted in accordance with the Army Policy for Use of Human Cadavers for RDT&E, Education, or Training, 20 April 2012 (https://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.overview).

The USAMRMC Office of Research Protections (ORP) is the Action Office (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil) for this policy. Approval must be obtained from the USAMRMC ORP. Award recipients must coordinate with the supporting/funding Army organization to ensure that proper approvals are obtained. ORP will issue written approvals to begin under separate notification to the recipient. Written approval to proceed from the USAMRMC ORP is also required for any subrecipient that will use funds from this award to conduct RDT&E, education or training involving human cadaveric specimens.

Recipients must promptly report problems related to the conduct of the activity involving cadavers or the procurement, inventory, use, storage, transfer, transportation, and disposition of cadavers to the USAMRMC ORP.

Recipients must maintain complete records of the activity.

The USAMRMC or designees must be permitted to observe the activity upon request and/or audit activity records to ensure compliance with the approved protocol or applicable regulatory requirements.

Non-compliance with these terms and conditions may result in withholding of funds and/or the termination of the award.

18. Interim Progress Review

In addition to quarterly, annual, and final technical progress reports, the PI shall prepare for and participate in at least one Interim Progress Review (IPR) for each year of the project's term of award. Generally, the IPR will last no longer than two days and require no more than two overnight stays. It most likely will be held in the Fort Detrick, Maryland area, but may occur elsewhere in the U.S. The invitation and format for the IPR will be provided by the GOR at least 90 days prior to the scheduled date.

19. Clinical Trial Registry

Certain clinical trials are required by U.S. law to be registered on the National Institutes of Health database entitled "ClinicalTrials.gov." For those trials required to be registered (see http://prsinfo.clinicaltrials.gov/, "Support Materials, including Data Element Definitions"), PIs must register clinical trials individually on http://www.clinicaltrials.gov. PIs must use a Secondary Protocol ID number designation of "CDMRP-OR160026". If several protocols exist under the same application, the Secondary Protocol ID number must be designated "CDMRP- OR160026-A, B, C, etc.". Clinical trials must be registered prior to enrollment of the first patient. Failure to do so may result in a civil monetary penalty and/or the withholding or recovery of award funds as per U.S. Public Law 110-85.

20. Required Start Date for Proposed Clinical Trial
The proposed clinical trial, a FDA-regulated study, is required to begin no later than 29 September 2018. Non-compliance with this term and condition may result in withholding of funds and/or the termination of the award.

RESEARCH & RELATED BUDGET - Budget Period 1

OMB Number: 4040-0001
Expiration Date: 10/31/2019

ORGANIZATIONAL DUNS: 2076639150000 **Enter name of Organization:** The Governors of the University of Calgary

Budget Type: ☒ Project ☐ Subaward/Consortium **Budget Period:** 1 **Start Date:** 01/01/2018 **End Date:** 12/31/2018

A. Senior/Key Person

Prefix	First	Middle	Last	Suffix	Base Salary ($)	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
Dr.	Kevin	Arnold	Hildebrand	MD		1.00			0.00	0.00	0.00
Project Role:	PD/PI										
Mrs.	Tanya		Harrison		58,500.00	6.00			29,250.00	6,435.00	35,685.00
Project Role:	Other Professional										
Ms.	Alexandra		Garven		37,060.00	6.00			18,530.00	4,818.00	23,348.00
Project Role:	Other Professional										
Dr.	Tolulope	Timothy	Sajobi	PhD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Nicholas	GH	Mohtadi	MD, MSc		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Prism	S	Schneider	MD, PhD		1.00			0.00	0.00	0.00
Project Role:	Co-PI/PD										
Dr.	Richard	EA	Walker	MD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Neil	J	White	MD		1.00			0.00	0.00	0.00
Project Role:	Site PI - SHC										

Additional Senior Key Persons: Additional Senior Key Persons.pd | Add Attachment | Delete Attachment | View Attachment

Total Funds requested for all Senior Key Persons in the attached file: 0.00

Total Senior/Key Person: 59,033.00

B. Other Personnel

Number of Personnel	Project Role	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
	Post Doctoral Associates						
1	Graduate Students	12.00			20,343.00	2,260.00	22,603.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Study Coordinator - Alex Garven PLC	6.00			18,530.00	4,818.00	23,348.00
1	Study Coordinator - PLC TBA	0.72			2,226.00	579.00	2,805.00
1	Study Coordinator - FMC Leah Schultz	9.22			28,536.00	4,987.00	33,523.00
1	Study Cooridnator - SHC Tina Samuel	3.39			9,286.00	2,414.00	11,700.00
1	Study Coordinator - RGH Saboura Mahdavi	1.69			7,039.00	1,830.00	8,869.00

6 Total Number Other Personnel

Total Other Personnel 102,848.00

Total Salary, Wages and Fringe Benefits (A+B) 161,881.00

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment item	Funds Requested ($)

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

Total funds requested for all equipment listed in the attached file

Total Equipment

D. Travel

	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	14,263.00
2. Foreign Travel Costs	
Total Travel Cost	14,263.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	1,000.00
2.	Stipends	
3.	Travel	2,000.00
4.	Subsistence	
5.	Other	
1	Number of Participants/Trainees	Total Participant/Trainee Support Costs: 3,000.00

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	219,858.00
2.	Publication Costs	2,712.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	134,969.00
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.	Participant Parking	6,615.00
9.	Participant Beverage/Food card	1,283.00
10.	Investigational Drug Service	8,303.00
	Total Other Direct Costs	373,740.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	552,884.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
Salary and Fringe benefits	39.80	161,881.00	64,429.00

Total Indirect Costs	64,429.00

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	617,313.00

J. Fee

Funds Requested ($)

K. Total Costs and Fee

	Funds Requested ($)
Total Costs and Fee (I + J)	617,313.00

L. Budget Justification

(Only attach one file.) Budget justification September 2017 f: | Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED BUDGET - Budget Period 2

OMB Number: 4040-0001
Expiration Date: 10/31/2019

ORGANIZATIONAL DUNS: 2076639150000 **Enter name of Organization:** The Governors of the University of Calgary

Budget Type: ☒ Project ☐ Subaward/Consortium **Budget Period: 2** **Start Date:** 01/01/2019 **End Date:** 12/31/2019

A. Senior/Key Person

Prefix	First	Middle	Last	Suffix	Base Salary ($)	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
Dr.	Kevin	Arnold	Hildebrand	MD		1.00			0.00	0.00	0.00
Project Role:	PD/PI										
Mrs.	Tanya		Harrison		60,254.00	6.00			30,127.00	6,628.00	36,755.00
Project Role:	Other Professional										
Ms.	Alexandra		Garven		38,172.00	6.00			19,086.00	4,962.00	24,048.00
Project Role:	Other Professional										
Dr.	Tolulope	Timothy	Sajobi	PhD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Nicholas	GH	Mohtadi	MD, MSc		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Prism	S	Schneider	MD, PhD		1.00			0.00	0.00	0.00
Project Role:	Co-PI/PD										
Dr.	Richard	EA	Walker	MD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Neil	J	White	MD		1.00			0.00	0.00	0.00
Project Role:	Site PI - SHC										

Additional Senior Key Persons: Additional Senior Key Persons.pd [Add Attachment] [Delete Attachment] [View Attachment]

Total Funds requested for all Senior Key Persons in the attached file 0.00

Total Senior/Key Person 60,803.00

B. Other Personnel

Number of Personnel	Project Role	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
	Post Doctoral Associates						
1	Graduate Students	12.00			20,343.00	2,260.00	22,603.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Study Coordinator - PLC Alex Garven	6.00			19,086.00	4,962.00	24,048.00
1	Study Coordinator - PLC TBA	3.10			9,855.00	2,562.00	12,417.00
1	Study Coordinator - FMC Leah Schultz	10.39			33,140.00	5,794.00	38,934.00
1	Study Coordinator - SHC Tina Samuel	3.98			13,060.00	3,395.00	16,455.00
1	Study Coordinator - RGH Saboura Mahdavi	3.35			14,360.00	3,734.00	18,094.00

6 Total Number Other Personnel

Total Other Personnel 132,551.00

Total Salary, Wages and Fringe Benefits (A+B) 193,354.00

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment item	Funds Requested ($)

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

Total funds requested for all equipment listed in the attached file

Total Equipment

D. Travel

	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	14,263.00
2. Foreign Travel Costs	
Total Travel Cost	14,263.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	1,000.00
2.	Stipends	
3.	Travel	2,000.00
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees — Total Participant/Trainee Support Costs	3,000.00

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	182,193.00
2.	Publication Costs	450.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	208,849.00
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.	Participant Parking	12,105.00
9.	Participant Beverage/Food card	2,558.00
10.	Investigational Drug Service	5,963.00
	Total Other Direct Costs	412,118.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	622,735.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
Salary and Fringe benefits	39.80	193,354.00	76,955.00

Total Indirect Costs	76,955.00

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	699,690.00

J. Fee

Funds Requested ($)

K. Total Costs and Fee

	Funds Requested ($)
Total Costs and Fee (I + J)	699,690.00

L. Budget Justification

(Only attach one file.) Budget justification September 2017 f: | Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED BUDGET - Budget Period 3

OMB Number: 4040-0001-
Expiration Date: 10/31/2019

ORGANIZATIONAL DUNS: 2076639150000 **Enter name of Organization:** The Governors of the University of Calgary

Budget Type: ☒ Project ☐ Subaward/Consortium **Budget Period:** 3 **Start Date:** 01/01/2020 **End Date:** 12/31/2020

A. Senior/Key Person

Prefix	First	Middle	Last	Suffix	Base Salary ($)	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
Dr.	Kevin	Arnold	Hildebrand	MD		1.00			0.00	0.00	0.00
Project Role:	PD/PI										
Mrs.	Tanya		Harrison		62,062.00	6.00			31,031.00	6,827.00	37,858.00
Project Role:	Other Professional										
Ms.	Alexandra		Garven		39,316.00	6.00			19,658.00	5,111.00	24,769.00
Project Role:	Other Professional										
Dr.	Tolulope	Timothy	Sajobi	PhD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Nicholas	GH	Mohtadi	MD, MSc		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Prism	S	Schneider	MD, PhD		1.00			0.00	0.00	0.00
Project Role:	Co-PI/PD										
Dr.	Richard	EA	Walker	MD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Neil	J	White	MD		1.00			0.00	0.00	0.00
Project Role:	Site PI - SHC										

Additional Senior Key Persons: Additional Senior Key Persons.pd [Add Attachment] [Delete Attachment] [View Attachment]

Total Funds requested for all Senior Key Persons in the attached file: 0.00

Total Senior/Key Person: 62,627.00

B. Other Personnel

Number of Personnel	Project Role	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
	Post Doctoral Associates						
1	Graduate Students	12.00			20,343.00	2,260.00	22,603.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Study Coordinator - PLC Alex Garven	6.00			19,658.00	5,111.00	24,769.00
1	Study Coordinator - PLC TBA	2.83			9,282.00	2,414.00	11,696.00
1	Study Coordinator - FMC Leah Schultz	11.94			39,239.00	6,859.00	46,098.00
1	Study Coordinator - SHC Tina Samuel	5.38			18,206.00	4,733.00	22,939.00
1	Study Coordinator - RGH Saboura Mahdavi	3.35			14,792.00	3,846.00	18,638.00

6 **Total Number Other Personnel**

Total Other Personnel 146,743.00

Total Salary, Wages and Fringe Benefits (A+B) 209,370.00

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment item	Funds Requested ($)

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

Total funds requested for all equipment listed in the attached file

Total Equipment

D. Travel

	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	16,763.00
2. Foreign Travel Costs	
Total Travel Cost	16,763.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	1,000.00
2.	Stipends	
3.	Travel	2,000.00
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees — Total Participant/Trainee Support Costs	3,000.00

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	182,193.00
2.	Publication Costs	450.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	199,178.00
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.	Participant Parking	12,900.00
9.	Participant Beverage/Food card	2,783.00
10.	Investigational Drug Service	5,805.00
	Total Other Direct Costs	403,309.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	632,442.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
Salary and Fringe benefits	39.80	209,370.00	83,330.00

Total Indirect Costs	83,330.00

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	715,772.00

J. Fee

	Funds Requested ($)

K. Total Costs and Fee

	Funds Requested ($)
Total Costs and Fee (I + J)	715,772.00

L. Budget Justification

(Only attach one file.) Budget justification September 2017 f: | Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED BUDGET - Budget Period 4

OMB Number: 4040-0001
Expiration Date: 10/31/2019

ORGANIZATIONAL DUNS: 2076639150000 **Enter name of Organization:** The Governors of the University of Calgary

Budget Type: ☒ Project ☐ Subaward/Consortium **Budget Period:** 4 **Start Date:** 01/01/2021 **End Date:** 12/31/2021

A. Senior/Key Person

Prefix	First	Middle	Last	Suffix	Base Salary ($)	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
Dr.	Kevin	Arnold	Hildebrand	MD		1.00			0.00	0.00	0.00
Project Role:	PD/PI										
Mrs.	Tanya		Harrison		63,924.00	6.00			31,962.00	7,032.00	38,994.00
Project Role:	Other Professional										
Ms.	Alexandra		Garven		40,496.00	6.00			20,248.00	5,264.00	25,512.00
Project Role:	Other Professional										
Dr.	Tolulope	Timothy	Sajobi	PhD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Nicholas	GH	Mohtadi	MD, MSc		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Prism	S	Schneider	MD, PhD		1.00			0.00	0.00	0.00
Project Role:	Co-PI/PD										
Dr.	Richard	EA	Walker	MD		1.00			0.00	0.00	0.00
Project Role:	Co-Investigator										
Dr.	Neil	J	White	MD		1.00			0.00	0.00	0.00
Project Role:	Site PI - SHC										

Additional Senior Key Persons: Additional Senior Key Persons.pd [Add Attachment] [Delete Attachment] [View Attachment]

Total Funds requested for all Senior Key Persons in the attached file: 0.00

Total Senior/Key Person: 64,506.00

B. Other Personnel

Number of Personnel	Project Role	Months Cal.	Months Acad.	Months Sum.	Requested Salary ($)	Fringe Benefits ($)	Funds Requested ($)
	Post Doctoral Associates						
1	Graduate Students	12.00			20,343.00	2,260.00	22,603.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Study Coordinator - PLC Alex Garven	2.43			8,185.00	2,128.00	10,313.00
1	Study Coordinator - FMC Leah Schultz	7.56			25,566.00	4,468.00	30,034.00
1	Study Coordinator - SHC Tina Samuel	1.41			4,911.00	1,277.00	6,188.00
1	Study Coordinator - RGH Saboura Mahdavi	0.72			3,274.00	851.00	4,125.00

5 **Total Number Other Personnel**

Total Other Personnel 73,263.00

Total Salary, Wages and Fringe Benefits (A+B) 137,769.00

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment item	Funds Requested ($)

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

Total funds requested for all equipment listed in the attached file

Total Equipment

D. Travel

	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	14,263.00
2. Foreign Travel Costs	
Total Travel Cost	14,263.00

E. Participant/Trainee Support Costs

	Funds Requested ($)
1. Tuition/Fees/Health Insurance	1,000.00
2. Stipends	
3. Travel	2,000.00
4. Subsistence	
5. Other	
Total Participant/Trainee Support Costs	3,000.00

Number of Participants/Trainees

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	118,815.00
2.	Publication Costs	2,712.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	69,465.00
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.	Participant Parking	4,290.00
9.	Participant Beverage/Food card	1,074.00
10.	Investigational Drug Services	1,800.00
	Total Other Direct Costs	198,156.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	353,188.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)
Salary and Fringe benefits	39.80	137,769.00	54,833.00

Total Indirect Costs	54,833.00

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	408,021.00

J. Fee

Funds Requested ($)

K. Total Costs and Fee

	Funds Requested ($)
Total Costs and Fee (I + J)	408,021.00

L. Budget Justification

(Only attach one file.) Budget justification September 2017 f: | Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		246,969.00
Section B, Other Personnel		455,405.00
Total Number Other Personnel	23	
Total Salary, Wages and Fringe Benefits (A+B)		702,374.00
Section C, Equipment		
Section D, Travel		59,552.00
1. Domestic	59,552.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		12,000.00
1. Tuition/Fees/Health Insurance	4,000.00	
2. Stipends		
3. Travel	8,000.00	
4. Subsistence		
5. Other		
6. Number of Participants/Trainees	1	
Section F, Other Direct Costs		1,387,323.00
1. Materials and Supplies	703,059.00	
2. Publication Costs	6,324.00	
3. Consultant Services	-	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	612,461.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	35,910.00	
9. Other 2	7,698.00	
10. Other 3	21,871.00	
Section G, Direct Costs (A thru F)		2,161,249.00
Section H, Indirect Costs		279,547.00
Section I, Total Direct and Indirect Costs (G + H)		2,440,796.00
Section J, Fee		
Section K, Total Costs and Fee (I + J)		2,440,796.00

COLLEGES AND UNIVERSITIES RATE AGREEMENT

EIN:

ORGANIZATION:
University of Calgary
2500 University Drive, N.W.
Fin. Rept. Admin.Bldg. Rm. #201
Calgary, Alberta, Canada T2N1N4

DATE: 09/19/2016

FILING REF.: The preceding agreement was dated 12/04/2012

The rates approved in this agreement are for use on grants, contracts and other agreements with the Federal Government, subject to the conditions in Section III.

SECTION I: Facilities And Administrative Cost Rates

RATE TYPES: FIXED FINAL PROV. (PROVISIONAL) PRED. (PREDETERMINED)

	EFFECTIVE PERIOD				
TYPE	FROM	TO	RATE(%)	LOCATION	APPLICABLE TO
PRED.	04/01/2016	03/31/2019	39.80	On-Campus	All Programs
PROV.	04/01/2019	Until Amended			Use same rates and conditions as those cited for fiscal year ending March 31, 2019.

*BASE

Direct salaries and wages including vacation, holiday, sick pay and other paid absences but excluding all other fringe benefits.

ORGANIZATION: University of Calgary

AGREEMENT DATE: 9/19/2016

SECTION II: SPECIAL REMARKS

TREATMENT OF FRINGE BENEFITS:

Fringe benefits applicable to direct salaries and wages are treated as direct costs.

TREATMENT OF PAID ABSENCES

Vacation, holiday, sick leave pay and other paid absences are included in salaries and wages and are claimed on grants, contracts and other agreements as part of the normal cost for salaries and wages. Separate claims are not made for the cost of these paid absences.

In accordance with HHS Grants Policy Directive, Part 3.01.C, no indirect cost is awarded on grants from the Department of Health and Human Services.

Equipment means an article of nonexpendable, tangible personal property having a useful life of more than one year and an acquisition cost of $5,000 or more per unit.

Your next proposal based on actual costs for the fiscal year ending 03/31/18 is due in our office by 09/30/18.

ORGANIZATION: University of Calgary

AGREEMENT DATE: 9/19/2016

SECTION III: GENERAL

A. LIMITATIONS:

The rates in this Agreement are subject to any statutory or administrative limitations and apply to a given grant, contract or other agreement only to the extent that funds are available. Acceptance of the rates is subject to the following conditions: (1) Only costs incurred by the organization were included in its facilities and administrative cost pools as finally accepted; such costs are legal obligations of the organization and are allowable under the governing cost principles; (2) The same costs that have been treated as facilities and administrative costs are not claimed as direct costs; (3) Similar types of costs have been accorded consistent accounting treatment; and (4) The information provided by the organization which was used to establish the rates is not later found to be materially incomplete or inaccurate by the Federal Government. In such situations the rate(s) would be subject to renegotiation at the discretion of the Federal Government.

B. ACCOUNTING CHANGES:

This Agreement is based on the accounting system purported by the organization to be in effect during the Agreement period. Changes to the method of accounting for costs which affect the amount of reimbursement resulting from the use of this Agreement require prior approval of the authorized representative of the cognizant agency. Such changes include, but are not limited to, changes in the charging of a particular type of cost from facilities and administrative to direct. Failure to obtain approval may result in cost disallowances.

C. FIXED RATES:

If a fixed rate is in this Agreement, it is based on an estimate of the costs for the period covered by the rate. When the actual costs for this period are determined, an adjustment will be made to a rate of a future year(s) to compensate for the difference between the costs used to establish the fixed rate and actual costs.

D. USE BY OTHER FEDERAL AGENCIES:

The rates in this Agreement were approved in accordance with the authority in Title 2 of the Code of Federal Regulations, Part 200 (2 CFR 200), and should be applied to grants, contracts and other agreements covered by 2 CFR 200, subject to any limitations in A above. The organization may provide copies of the Agreement to other Federal Agencies to give them early notification of the Agreement.

E. OTHER:

If any Federal contract, grant or other agreement is reimbursing facilities and administrative costs by a means other than the approved rate(s) in this Agreement, the organization should (1) credit such costs to the affected programs, and (2) apply the approved rate(s) to the appropriate base to identify the proper amount of facilities and administrative costs allocable to these programs.

BY THE INSTITUTION:

University of Calgary

(INSTITUTION)

(SIGNATURE)

Brad Klaiber

(NAME)

Director, Financial Reporting

(TITLE)

March 2, 2017

(DATE)

ON BEHALF OF THE FEDERAL GOVERNMENT:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

(AGENCY)

Darryl W. Mayes -S Digitally signed by Darryl W. Mayes -S
DN: c=US, o=U.S. Government, ou=HHS, ou=PIV, ou=People, 0.9.2342.19200300.100.1.1=70001316481, cn=Darryl W. Mayes -S
Date: 2016.09.21 10:50:21 -04'00'

(SIGNATURE)

Darryl W. Mayes

(NAME)

Deputy Director, Cost Allocation Services

(TITLE)

9/19/2016

(DATE) 0400

HHS REPRESENTATIVE: Edwin Miranda

Telephone: (212) 264-2069

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (58.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
June 30, 2019-	1,815.00	1067.22	180.00	0	30.00	0	1,350.00	0	
September 30, 2019-	3,170.00	1863.96	360.00	0	70.00	0	350.00	0	
December 30, 2019-	3,420.00	2010.96	400.00	0	80.00	0	350.00	0	
TOTAL	8,405.00	4,942.14	940.00	0.00	180.00	0.00	2,050.00	0.00	16,527.14

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (58.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2020-	4,025.00	2366.7	460.00	0.00	90.00	0.00	460.00	0.00	
June 30, 2020-	5,025.00	2954.7	620.00	0.00	130.00	0.00	400.00	0.00	
September 30, 2020-	5,275.00	3101.7	660.00	0.00	140.00	0.00	400.00	0.00	
December 30, 2020-	4,670.00	2745.96	600.00	0.00	130.00	0.00	350.00	0.00	
TOTAL	18,995.00	11,169.06	2,340.00	0.00	490.00	0.00	1,610.00	0.00	34,604.06

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (58.8%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2021-	2,250.00	1323	360.00	0.00	90.00	0.00	150.00	0.00	
June 30, 2021-	1,250.00	735	200.00	0.00	50.00	0.00	150.00	0.00	
September 30, 2021-	1,250.00	735	200.00	0.00	50.00	0.00	150.00	0.00	
December 30, 2021-	1,000.00	588	160.00	0.00	40.00	0.00	450.00	0.00	
TOTAL	5,750.00	3,381.00	920.00	0.00	230.00	0.00	900.00	0.00	11,181.00

TOTAL BUDGET: $62,312.20 CAD which includes Study Coordinator time, Participant parking and Food/Boverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q3	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 3 participants x $250/participant =	$750
			C$3,170
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 4 participants x $250/participant =	$1,000
			C$3,420
Year 2020:	Q1	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 4 participants x $250/participant =	$1,000
			C$4,025
	Q2	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 3 participants x $250/participant =	$750
			C$5,025
	Q3	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$5,275
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$4,670
Year 2021:	Q1	12 weeks - 4 participants x $250/participant =	$1,000
		52 weeks – 5 participants x $250/participant =	$1,250
			C$2,250
	Q2	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q3	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q4	52 weeks – 4 participants x $250/participant =	$1,000
			C$1,000

Participant Parking:

Year 2019:	Q2	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q3	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 3 participants x $40/participant =	$120
			C$360
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 4 participants x $40/participant =	$160
			C$400
Year 2020:	Q1	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 4 participants x $40/participant =	$160
			C$460
	Q2	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 3 participants x $40/participant =	$120
			C$620
	Q3	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$660
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$600
Year 2021:	Q1	12 weeks - 4 participants x $40/participant =	$160
		52 weeks – 5 participants x $40/participant =	$200
			C$360
	Q2	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q3	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q4	52 weeks – 4 participants x $40/participant =	$160
			C$160

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q3	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 3 participants x $10/participant =	$30
			C$70
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 4 participants x $10/participant =	$40
			C$80
Year 2020:	Q1	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 4 participants x $10/participant =	$40
			C$90
	Q2	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 3 participants x $10/participant =	$30
			C$130

	Q3	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$140
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$130
Year 2021:	Q1	12 weeks - 4 participants x $10/participant =	$40
		52 weeks – 5 participants x $10/participant =	$50
			C$90
	Q2	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q3	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q4	52 weeks – 4 participants x $10/participant =	$40
			C$40

Investigational Drug Service (Using Dalhousie template)

Year 2019:	Q2	Start Up Fee	=	$1,000
		Maintenance Fee -	=	$150
		Dispensing fee – 3 participants x $50/participant =		$150
		Monitoring visit	=	$60
				C$1,360
	Q3	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
	Q4	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
Year 2020:	Q1	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
		Monitoring visit	=	$60
				C$460
	Q2	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
				C$400
	Q3	Maintenance Fee -	=	$150
		Dispensing fee – 5 participants x $50/participant =		$250
				C$400
	Q4	Maintenance Fee -	=	$150
		Dispensing fee – 4 participants x $50/participant =		$200
				C$350
Year 2021:	Q1	Maintenance Fee -	=	$150
				C$150
	Q2	Maintenance Fee -	=	$150
				C$150
	Q3	Maintenance Fee -	=	$150
				C$150
	Q4	Maintenance Fee -	=	$150
		Close-out Fee	=	$300
				C$450

H. INDIRECT COSTS

1. General & Administrative:

The indirect cost agreement of the University of British Columbia is 58.8%. All salaries and wages, and fringe benefits are included in the calculation. The participant support costs such as parking and beverage/food cards, and the Investigational Drug Services, are not included.

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. J Whitcomb Pollock
The Ottawa Hospital-General Campus
501 Smyth Road, Room W 1644
Ottawa, Ontario K1H 8L6
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Ottawa Hospital Research Institute
725 Parkdale Avenue, Ottawa, Ontario, Canada, K1Y 4E9

(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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study

case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the drug ("Study Drug") and placebo ("Placebo") at no charge to SUB INSTITUTION and SUB INVESTIGATOR in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB

INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: Ottawa Hospital Research Institute

Address of Payee: Dr. J Pollock c/o Katie McIlquham
Orthopaedic Research Office
501 Smyth Road, Room W1636, Box #502
Ottawa, ON K1H 8L6

2.3 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study (including PRINCIPAL INSTITUTION'S name as sponsor, name of the study, protocol number, and funding amount) as required by law, court order, or regulation; or in (1) SUB INVESTIGATOR's C.V.; (2) their respective

websites; (3) industry directories; (4) brochures and marketing materials; (5) internal reports; (6) financial reporting; (7) publications and presentations; (8) grant applications to government funding sources; (9) government reports and filings; and (10) conflict- of-interest reports. This paragraph also applies to sub-investigators and other study personnel..

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (30) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUBINSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in

conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees or appointees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta),*Personal Health Information Protection Act* (Ontario), and any other substantially similar provincial legislation to which the applicable Party is bound to comply; (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any applicable law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. Each of PRINCIPAL INSTITUTION and SUB INSTITUTION shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations

under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The PRINCIPAL INSTITUTION has entered into an agreement with Bay Area Research Logistics (BARL) in order to procure the Study Drug and Placebo. The PRINCIPAL INSTITUTION represents and warrants that its agreement with BARL provides as follows:

BARL will perform all packaging and logistical operations in accordance with GMP standards. An appropriate level of QA and QC checks will be determined and implemented. BARL will prepare all relevant documentation. BARL shall indemnify and hold harmless the Sponsor and any institutions participating in the Study for any third party claims arising from the negligence or wilful misconduct of BARL in respect of the scope of work contained within this Agreement.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and, except where the SUB INVESTIGATOR is ceasing his/her participation in the Clinical Study for reasons

related to the safety of his/her patients, will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. J Whitcomb Pollock
The Ottawa Hospital-General Campus
Orthopaedic Surgery
501 Smyth Road, Room Room W1636, Box #502
Ottawa, ON K1H 8L6

Phone: 613-737-3031
Email: jpollock@toh.ca

to the SUB INSTITUTION:

Ottawa Hospital Research Institute
c/o Marisa Akow, Director of Research Administration
725 Parkdale Avenue
Ottawa, Ontario K1Y 4E9
Email: makow@ohri.ca

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Ontario and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ September 10 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ SEP 12 2019

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____ 2019/9/10

Date

SUB INSTITUTION:

Authorized

Signatures: _____ Sept. 10/19

Date

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (40%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
June 30, 2019-	3,630.00	1452	360.00	0.00	60.00	0	2,192.00	0	
September 30, 2019-	6,340.00	2536	720.00	0.00	140.00	0	136.00	0	
December 30, 2019-	6,840.00	2736	800.00	0.00	160.00	0	136.00	0	
TOTAL	16,810.00	6,724.00	1,880.00	0.00	360.00	0.00	2,464.00	0.00	28,238.00

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (40%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2020-	8,050.00	3220	920.00	0.00	180.00	0.00	988.00	0.00	
June 30, 2020-	10,050.00	4020	1,240.00	0.00	260.00	0.00	170.00	0.00	
September 30, 2020-	10,550.00	4220	1,320.00	0.00	280.00	0.00	170.00	0.00	
December 30, 2020-	9,340.00	3736	1,200.00	0.00	260.00	0.00	136.00	0.00	
TOTAL	37,990.00	15,196.00	4,680.00	0.00	980.00	0.00	1,464.00	0.00	60,310.00

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (40%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2021-	4,500.00	1800	720.00	0.00	180.00	0.00	744.00	0.00	
June 30, 2021-	2,500.00	1000	400.00	0.00	100.00	0.00	0.00	0.00	
September 30, 2021-	2,500.00	1000	400.00	0.00	100.00	0.00	0.00	0.00	
December 30, 2021-	2,000.00	800	320.00	0.00	80.00	0.00	212.00	0.00	
TOTAL	11,500.00	4,600.00	1,840.00	0.00	460.00	0.00	956.00	0.00	19,356.00

TOTAL BUDGET: $107,904.00 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee-for-service on a per-participant basis, invoice based.

107,904.00

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment – 6 participants x $605/participant =	$3,630
			C$3,630
	Q3	Enrollment – 8 participants x $605/participant =	$4,840
		12 weeks – 6 participants x $250/participant =	$1,500
			C$6,340
	Q4	Enrollment – 8 participants x $605/participant =	$4,840
		12 weeks – 8 participants x $250/participant =	$2,000
			C$6,840
Year 2020:	Q1	Enrollment – 10 participants x $605/participant =	$6,050
		12 weeks – 8 participants x $250/participant =	$2,000
			C$8,050
	Q2	Enrollment – 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 6 participants x $250/participant =	$1,500
			C$10,050
	Q3	Enrollment – 10 participants x $605/participant =	$6,050
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 8 participants x $250/participant =	$2,000
			C$10,550
	Q4	Enrollment – 8 participants x $605/participant =	$4,840
		12 weeks – 10 participants x $250/participant =	$2,500
		52 weeks – 8 participants x $250/participant =	$2,000
			C$9,340
Year 2021:	Q1	12 weeks – 8 participants x $250/participant =	$2,000
		52 weeks – 10 participants x $250/participant =	$2,500
			C$4,500
	Q2	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q3	52 weeks – 10 participants x $250/participant =	$2,500
			C$2,500
	Q4	52 weeks – 8 participants x $250/participant =	$2,000
			C$2,000

Participant Parking:

Year 2019:	Q2	Enrollment – 6 participants x $60/participant =	$360
			C$360
	Q3	Enrollment – 8 participants x $60/participant =	$480
		12 weeks – 6 participants x $40/participant =	$240
			C$720
	Q4	Enrollment – 8 participants x $60/participant =	$480
		12 weeks – 8 participants x $40/participant =	$320
			C$800
Year 2020:	Q1	Enrollment – 10 participants x $60/participant =	$600
		12 weeks – 8 participants x $40/participant =	$320
			C$920
	Q2	Enrollment – 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 6 participants x $40/participant =	$240
			C$1240
	Q3	Enrollment – 10 participants x $60/participant =	$600
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 8 participants x $40/participant =	$320
			C$1320
	Q4	Enrollment – 8 participants x $60/participant =	$480
		12 weeks – 10 participants x $40/participant =	$400
		52 weeks – 8 participants x $40/participant =	$320
			C$1200
Year 2021:	Q1	12 weeks – 8 participants x $40/participant =	$320
		52 weeks – 10 participants x $40/participant =	$400
			C$720
	Q2	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q3	52 weeks – 10 participants x $40/participant =	$400
			C$400
	Q4	52 weeks – 8 participants x $40/participant =	$320
			C$320

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment – 6 participants x $10/participant =	$60
			C$60
	Q3	Enrollment – 8 participants x $10/participant =	$80
		12 weeks – 6 participants x $10/participant =	$60
			C$140
	Q4	Enrollment – 8 participants x $10/participant =	$80
		12 weeks – 8 participants x $10/participant =	$80
			C$160
Year 2020:	Q1	Enrollment – 10 participants x $10/participant =	$100
		12 weeks – 8 participants x $10/participant =	$80
			C$180
	Q2	Enrollment – 10 participants x $10/participant =	$100

		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 6 participants x $10/participant =	$60
			C$260
	Q3	Enrollment – 10 participants x $10/participant =	$100
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 8 participants x $10/participant =	$80
			C$280
	Q4	Enrollment – 8 participants x $10/participant =	$80
		12 weeks – 10 participants x $10/participant =	$100
		52 weeks – 8 participants x $10/participant =	$80
			C$260
Year 2021:	Q1	12 weeks – 8 participants x $10/participant =	$80
		52 weeks – 10 participants x $10/participant =	$100
			C$180
	Q2	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q3	52 weeks – 10 participants x $10/participant =	$100
			C$100
	Q4	52 weeks – 8 participants x $10/participant =	$80
			C$80

Investigational Drug Service

Year 2019:	Q2	Start Up Fee	=	$1,272
		Maintenance Fee –	=	$636
		Dispensing fee – 6 participants x $17/participant =		$102
		Drug destruction	=	$108
		Monitoring visit	=	$74
				C$2,192
	Q3	Dispensing fee – 8 participants x $17/participant =		$136
				C$136
	Q4	Dispensing fee – 8 participants x $17/participant =		$136
				C$136
Year 2020:	Q1	Maintenance Fee –	=	$636
		Dispensing fee – 10 participants x $17/participant =		$170
		Drug destruction	=	$108
		Monitoring visit	=	$74
				C$988
	Q2	Dispensing fee – 10 participants x $17/participant =		$170
				C$170
	Q3	Dispensing fee – 10 participants x $17/participant =		$170
				C$170
	Q4	Dispensing fee – 8 participants x $17/participant =		$136
				C$136
Year 2021:	Q1	Maintenance Fee –	=	$636
		Drug destruction	=	$108
				C$744
	Q2			C$0
	Q3			C$0

Q4	Close-out Fee	=	$212
			C$212

H. INDIRECT COSTS

1. General & Administrative:

The rate at the Ottawa Hospital Research Institute is 40%. All salaries and wages, and applicable fringe benefits are included in the calculation. Participant support costs such as parking and beverage/food cards, and the Investigational Drug Service, are not included.

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. Raymond Pensy
620 West Lexington St. 4th Floor, Baltimore, Maryland 21201
(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

University of Maryland, Baltimore
(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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement. The Protocol may be amended from time to time with the

approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR and the SUB INSTITUTION shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records, study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall notify the PRINCIPAL INSTITUTION immediately upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall also provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall provide sufficient quantities of the Study Drug and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INSTITUTION shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INSTITUTION AND THE SUB INVESTIGATOR will destroy or return any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written confirmation of destruction is provided by the SUB INSTITUTION.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee:	University of Maryland, Baltimore
Address of Payee:	P.O. Box 41428 Baltimore, MD 21203-6428 **Please reference the Invoice number and PI on all payments**

2.3 Invoices shall be:

(i) Billed to:	The University of Calgary 2500 University Drive NW Calgary, Alberta, Canada T2N 1N4
and (ii) Sent to:	Attention: Dr. Kevin Hildebrand, PERK 2 Health Research Innovation Centre 3280 Hospital Drive NW

Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or presentation or eighteen (18) months after the database lock for the entire multicentre study, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (60) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 SUB INVESTIGATOR and SUBINSTITUTION agree to comply with section 11 of the Prime Agreement for Publication and if they wish to release any information relating to this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall notify the PRINCIPAL INSTITUTION and the Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information,

excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Government of Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of (a) their violation of any law or regulation; (b) their breach of this Agreement; or (c) their negligent or wrongful act or omission. PRINCIPAL INSTITUTION shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 SUB INSTITUTION falls under a state-funded self-insured pursuant to Annotated Code of Maryland, State Finance and Procurement Article, Title 9, as amended from time to time. SUB INSTITUTION will be responsible for its own negligence in accordance with the Maryland Tort Claims Act.

8.3 The PRINCIPAL INSTITUTION and SUB INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR

acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.6 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.7 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.8 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.9 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and if applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Raymond Pensy
Shock Trauma Center 3RD FLOOR
22 South Greene St.
Baltimore, Maryland, 21201
RPensy@som.umaryland.edu
410-328-6280

to the SUB INSTITUTION:

Dennis J. Paffrath, MBA
Associate Vice President, Research

620 W. Lexington Street, 4th Floor
Baltimore, MD 21201
410-706-1101
dpaffrat@umaryland.edu

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary
Legal, Research Services - CSM
Office G360, Ground Floor Health Sciences Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

Parties agree to remain silent on Governing Law.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of

which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ March 6, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:
THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ MAR 0 8 2019

Marcello Tonelli — Date
Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: _____ 2/26/19

Raymond Pensy — Date

SUB INSTITUTION:

Authorized Signatures: _____ 2/25/2019

Dennis Paffrath — Date

ATTACHMENT A
(Prime Agreement)
(Attached hereto)

ATTACHMENT B
(Protocol)
PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C
(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (54.5%)	Parking	Indirect (54.5%)	Beverage	Indirect (54.5%)	Pharmacy	Indirect (54.5%)	
June 30, 2019-	1,361.25	741.88	135.00	73.58	22.50	12.26	1,400.00	763.00	
September 30, 2019-	2,377.50	1295.74	270.00	147.15	52.50	28.61	450.00	245.25	
December 30, 2019-	2,565.00	1397.93	300.00	163.50	60.00	32.70	450.00	245.25	
TOTAL	6,303.75	3,435.54	705.00	384.23	135.00	73.58	2,300.00	1,253.50	14,590.59

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (54.5%)	Parking	Indirect (54.5%	Beverage	Indirect (54.5%)	Pharmacy	Indirect (54.5)	
March 30, 2020-	3,018.75	1645.22	345.00	188.03	67.50	36.79	500.00	272.50	
June 30, 2020-	3,768.75	2053.97	465.00	253.43	97.50	53.14	500.00	272.50	
September 30, 2020-	3,956.25	2156.16	495.00	269.78	105.00	57.23	500.00	272.50	
December 30, 2020-	3,502.50	1908.86	450.00	245.25	97.50	53.14	450.00	245.25	
TOTAL	14,246.25	7,764.21	1,755.00	956.48	367.50	200.29	1,950.00	1,062.75	28,302.47

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (54.5%)	Parking	Indirect (54.5%)	Beverage	Indirect (54.5%)	Pharmacy	Indirect (54.5%)	
March 30, 2021-	1,687.50	919.69	270.00	147.15	67.50	36.79	250.00	136.25	
June 30, 2021-	937.50	510.94	150.00	81.75	37.50	20.44	250.00	136.25	
September 30, 2021-	937.50	510.94	150.00	81.75	37.50	20.44	250.00	136.25	
December 30, 2021-	750.00	408.75	120.00	65.40	30.00	16.35	750.00	408.75	
TOTAL	4,312.50	2,350.31	690.00	376.05	172.50	94.01	1,500.00	817.50	10,312.88

MARYLAND TOTAL BUDGET: $53,205.94 US Dollars which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees and indirect costs. All payments are fee for service on a per participant basis, invoice based.

53,205.94

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815 x 0.75 = US$1,361.25
	Q3	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 3 participants x $250/participant =	$750
			C$3,170 x 0.75 = US$2,377.50
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 4 participants x $250/participant =	$1,000
			C$3,420 x 0.75 = US$2,565.00
Year 2020:	Q1	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 4 participants x $250/participant =	$1,000
			C$4,025 x 0.75 = US$3,018.75
	Q2	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 3 participants x $250/participant =	$750
			C$5,025 x 0.75 = US$3,768.75
	Q3	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$5,275 x 0.75 = US$3,956.25
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$4,670 x 0.75 = US$3,502.50
Year 2021:	Q1	12 weeks - 4 participants x $250/participant =	$1,000
		52 weeks – 5 participants x $250/participant =	$1,250
			C$2,250 x 0.75 = US$1,687.50
	Q2	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250 x 0.75 = US$937.50
	Q3	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250 x 0.75 = US$937.50
	Q4	52 weeks – 4 participants x $250/participant =	$1,000
			C$1,000 x 0.75 = US$750.00

Participant Parking:

Year 2019:	Q2	Enrollment - 3 participants x $60/participant =	$180
			C$180 x 0.75 = US$135.00
	Q3	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 3 participants x $40/participant =	$120
			C$360 x 0.75 = US$270.00
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 4 participants x $40/participant =	$160
			C$400 x 0.75 = US$300.00
Year 2020:	Q1	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 4 participants x $40/participant =	$160
			C$460 x 0.75 = US$345.00
	Q2	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 3 participants x $40/participant =	$120
			C$620 x 0.75 = US$465.00
	Q3	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$660 x 0.75 = US$495.00
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$600 x 0.75 = $450.00
Year 2021:	Q1	12 weeks - 4 participants x $40/participant =	$160
		52 weeks – 5 participants x $40/participant =	$200
			C$360 x 0.75 = US$270.00
	Q2	52 weeks – 5 participants x $40/participant =	$200
			C$200 x 0.75 = US$150.00
	Q3	52 weeks – 5 participants x $40/participant =	$200
			C$200 x 0.75 = US$150.00
	Q4	52 weeks – 4 participants x $40/participant =	$160
			C$160 x 0.75 = US$120.00

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment - 3 participants x $10/participant =	$30
			C$30 x 0.75 = US$22.50
	Q3	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 3 participants x $10/participant =	$30
			C$70 x 0.75 = US$52.50
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 4 participants x $10/participant =	$40
			C$80 x 0.75 = US$60.00
Year 2020:	Q1	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 4 participants x $10/participant =	$40
			C$90 x 0.75 = US$67.50
	Q2	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 3 participants x $10/participant =	$30
			C$130 x 0.75 = US$97.50

	Q3	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$140 x 0.75 = US$105.00
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$130 x 0.75 = US$97.50
Year 2021:	Q1	12 weeks - 4 participants x $10/participant =	$40
		52 weeks – 5 participants x $10/participant =	$50
			C$90 x 0.75 = US$67.50
	Q2	52 weeks – 5 participants x $10/participant =	$50
			C$50 x 0.75 = US$37.50
	Q3	52 weeks – 5 participants x $10/participant =	$50
			C$50 x 0.75 = US$37.50
	Q4	52 weeks – 4 participants x $10/participant =	$40
			C$40 x 0.75 = US$30.00

Investigational Drug Service (Using Carolinas template)

Year 2019:	Q2	Start Up Fee	=	$1,000
		Maintenance Fee -	=	$250
		Dispensing fee – 3 participants x $50/participant =		$150
				US$1,400
	Q3	Maintenance Fee -	=	$250
		Dispensing fee – 4 participants x $50/participant =		$200
				US$450
	Q4	Maintenance Fee -	=	$250
		Dispensing fee – 4 participants x $50/participant =		$200
				US$450
Year 2020:	Q1	Maintenance Fee -	=	$250
		Dispensing fee – 5 participants x $50/participant =		$250
				US$500
	Q2	Maintenance Fee -	=	$250
		Dispensing fee – 5 participants x $50/participant =		$250
				US$500
	Q3	Maintenance Fee -	=	$250
		Dispensing fee – 5 participants x $50/participant =		$250
				US$500
	Q4	Maintenance Fee -	=	$250
		Dispensing fee – 4 participants x $50/participant =		$200
				US$450
Year 2021:	Q1	Maintenance Fee -	=	$250
				US$250
	Q2	Maintenance Fee -	=	$250
				US$250
	Q3	Maintenance Fee -	=	$250
				US$250
	Q4	Maintenance Fee -	=	$250
		Close-out Fee	=	$500
				US$750

H. INDIRECT COSTS

1. General & Administrative:

The rate at the University of Maryland, Baltimore is 54.5%. All salaries and wages, and applicable fringe benefits are included in the calculation. Services are included and there is no specified exclusion of Participant support costs such as parking and beverage/food cards. Thus, Parking and Beverage/Food care services, and Investigational Drug Services are included.

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. Robert Koon Wah Chan (AKA Robert Chan)

6-110 Clinical Sciences Building, 11306 83 Avenue Northwest, University of Alberta, Edmonton, Alberta, Canada T6G 2G3

(the "SUB INVESTIGATOR")

OF THE THIRD PART,

-and-

Alberta Health Services ("AHS") and The Governors of the University of Alberta ("University")

Suite 400, 8215 – 112 Street, Edmonton, Alberta, Canada T6G 2C8

(Hereinafter AHS and University will be collectively referred to as the "SUB INSTITUTION" however the rights and obligations of each of AHS and University shall remain several and not joint)

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").

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 INVESTIGATOR and the SUB INSTITUTION have 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").

NOW THEREFORE THIS AGREEMENT WITNESSETH that in consideration of the covenants and obligations herein contained the Parties hereto covenant and agree with each other as follows:

1. Study Conduct

1.1 The SUB INSTITUTION and the SUB INVESTIGATOR hereby agree to conduct the Clinical Study as described in the Protocol as set out in ATTACHMENT B ("Protocol") in a timely manner and in strict accordance with this Agreement and the Protocol. The Protocol may be amended from time to time with the approval of the PRINCIPAL INVESTIGATOR and the applicable Research Ethics Board ("REB") and all future amendments incorporated into the Protocol shall form a part of this Agreement by reference. The SUB INSTITUTION and the SUB INVESTIGATOR will conduct the Clinical Study in conformance with generally accepted standards of good clinical practice, all applicable federal, provincial and local laws and regulations, the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, and the Second Edition of the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans.

Notwithstanding the foregoing, SUB INVESTIGATOR may, in accordance with applicable ICH Guidelines for Good Clinical Practice, where allowance is made for medically necessary variations to the Protocol by the REB, or as required for ethical medical practice, diverge from the Protocol to the extent required to address the medically necessary variation or ethical medical practice, and the SUB INVESTIGATOR shall immediately record any such divergence in the source document, promptly report the variation to PRINCIPAL INVESTIGATOR and, as necessary the REB, and any such variation shall not constitute a failure to follow the Protocol or more generally, a breach of this Agreement.

SUB INVESTIGATOR shall comply with all AHS and University policies, procedures and guidelines applicable to the conduct of the Study including, without limitation, policies and guidelines regarding Collection, Access, Use, and Disclosure of Information, Intellectual Property, Privacy, Records Management, Grants and Clinical Trial Funding. AHS research policies and guidelines are available at http://www.albertahealthservices.ca/research/8601.asp. University research policies and procedures are available at http://www.rso.ualberta.ca/en/PoliciesProcedures.aspx.

1.2 It is a condition of the obligations of the SUB INSTITUTION and the SUB INVESTIGATOR to conduct the Clinical Study becoming effective that:

(i) the PRINCIPAL INVESTIGATOR shall have provided all information required by the SUB INSTITUTION and the SUB INVESTIGATOR to obtain ethical and administrative approval for the Clinical Study; and

(ii) the SUB INVESTIGATOR shall have applied for and received all administrative and ethical approvals required for the conduct of the Clinical Study.

1.3 The SUB INSTITUTION and the SUB INVESTIGATOR shall permit the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR and/or the PRINCIPAL INSTITUTION's designee(s), including but not limited to PRINCIPAL INSTITUTION's REB, access to the SUB INSTITUTION and patient medical records, to monitor the conduct of the Clinical Study, to audit records (during regular business hours at mutually agreeable times), study case report forms ("CRFs"), source documents, and any other data relating to the Clinical Study, in order to comply with regulatory requirements and to verify the SUB INSTITUTION's and the SUB INVESTIGATOR's compliance with their obligations herein, provided however, that any such access is in accordance with the permissions granted in the participant informed consent form, if applicable, and applicable privacy laws.

1.4 If, as a result of Clinical Study monitoring, the PRINCIPAL INSTITUTION requests reasonable corrective and/or preventive action, the SUB INSTITUTION and the SUB INVESTIGATOR shall create and implement a corrective and/or preventive action plan in a timely manner.

1.5 Upon request by any properly authorized officer or employee of any regulatory authority, the SUB INSTITUTION and/or the SUB INVESTIGATOR shall permit such officer or employee to inspect the conduct of the Clinical Study, interview personnel, have access to, copy and verify documents relating to the Clinical Study, and shall produce such documents (or copies thereof) to such regulatory authority when required. SUB INSTITUTION and/or SUB INVESTIGATOR shall, where possible and to the extent legally permissible, notify the PRINCIPAL INSTITUTION promptly upon the receipt of a request for inspection of the Subsite by a regulatory authority. The SUB INSTITUTION shall, to the extent legally permissible, also

provide copies of all correspondence with a regulatory authority regarding any Study activities

1.6 The PRINCIPAL INSTITUTION shall in a timely manner provide sufficient quantities of the Study Drug and placebo in order for the SUB INSTITUTION to adequately perform the Clinical Study. The PRINCIPAL INSTITUTION shall provide any other materials or equipment such as shipping temperature thermometers as required by the SUB INSTITUTION to perform the Clinical Study. The SUB INVESTIGATOR shall comply with any directions or instructions provided by the PRINCIPAL INSTITUTION in connection with the storage, maintenance or disposal of the Study Drug. The Study Drug provided by the PRINCIPAL INSTITUTION shall be used exclusively for the performance of this Clinical Study and is to be used only by Clinical Study subjects ("Participants") under the SUB INVESTIGATOR's supervision, or under the supervision of another SUB INSTITUTION physician trained on the Protocol. At any time, at the PRINCIPAL INVESTIGATOR's request, the SUB INVESTIGATOR will destroy or return, at the PRINCIAPAL INSTITUTION's expense, any or all of the unused Study Drug. Study Drug will not be destroyed unless written instructions are provided by PRINCIPAL INVESTIGATOR or designate, and written notification of destruction is provided by the SUB INVESTIGATOR.

2. Consideration

2.1 Subject to the terms of this Agreement, as consideration for the conduct of the Clinical Study, the PRINCIPAL INSTITUTION shall pay to the SUB INSTITUTION as per ATTACHMENT C attached hereto (the "Payments"). Notwithstanding any provision to the contrary, payment is contingent upon (i) SUB INVESTIGATOR and SUB INSTITUTION's satisfactory completion of services required under the Protocol and this Agreement; and (ii) PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION's receipt of funds and continuing approval from the Funding Source provided that, if such funds are no longer available to PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION or such approval is withdrawn, SUB INVESTIGATOR and/or SUB INSTITUTION may terminate this agreement in accordance with Section 10 hereof.

2.2 Upon receipt of a correct and approved invoice from the SUB INSTITUTION, the PRINCIPAL INSTITUTION shall make the Payments by cheque payable to:

Name of Payee: Alberta Health Services

Address of Payee: Dr. Robert Chan, C/O Anelise Silveira, Project # 35558
6-110 Clinical Sciences Building, 11306 83 Avenue Northwest,
University of Alberta, Edmonton, Alberta, Canada T6G 2G3

AHS Tax Exempt Number: R124072513

2.3 Invoices shall be:

(i) Billed to: The University of Calgary
2500 University Drive NW
Calgary, Alberta, Canada T2N 1N4

and

(ii) Sent to: Attention: Dr. Kevin Hildebrand, PERK 2
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada
Email: hildebrk@ucalgary.ca

3. Publicity and Use of Names

The use by any Party of the name, trademark, trade name, logo, or any adaptation thereof, of any other Party in any publication, press release, advertisement, announcement, promotional material, or promotional activity relating to the Clinical Study requires the prior written consent of the affected Party, subject, however, to the following:

(a) the PRINCIPAL INSTITUTION and the PRINCIPAL INVESTIGATOR may, without prior consent, identify the SUB INSTITUTION as an entity that participated in the Clinical Study, and identify the SUB INVESTIGATOR as conducting the Clinical Study at the SUB INSTITUTION; and

(b) the SUB INSTITUTION and the SUB INVESTIGATOR may, without prior consent, disclose their participation in the Clinical Study to the extent as required by law, Court order, or regulation; (ii) SUB INVESTIGATOR's C.V.; (2) internal reports; (3) publications and presentations made in accordance with this Agreement; (4) grant applications to government funding sources; (5) government reports and filings; and (6) conflict-of-interest reports.

4. Publication

4.1 The SUB INVESTIGATOR and the SUB INSTITUTION agree to coordinate all publication of Clinical Study results with the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. The Parties agree that the first publication or presentation of the results of the Clinical Study will be made in conjunction with the

presentation of a joint, multicentre publication or presentation of the complete multicentre Clinical Study results. Upon such multicentre publication or presentation or twelve (12) months after the database lock for the entire multicentre study or the abandonment or termination of the Study at all Study sites, whichever occurs earlier, SUB INSTITUTION and the SUB INVESTIGATOR may publish or present data generated in its performance of the Clinical Study ("Proposed Publication") in accordance with the terms of this Section 4. SUB INSTITUTION or the SUB INVESTIGATOR shall forward the Proposed Publication to PRINCIPAL INVESTIGATOR at least thirty (30) days prior to the planned submission/presentation date. PRINCIPAL INVESTIGATOR will have no more than twenty (20) days after its receipt of the Proposed Publication to respond with any requested revisions. SUB INSTITUTION and the SUB INVESTIGATOR will consider in good faith such requested revisions and will delete, at PRINCIPAL INVESTIGATOR's request, any Confidential Information, as defined below, (excluding data/results or study methods sufficient for the requirements of an academic journal) from such Proposed Publication. Upon PRINCIPAL INVESTIGATOR's request, SUB INSTITUTION and the SUB INVESTIGATOR shall delay submission/presentation of such Proposed Publication for an additional sixty (60) days to permit the filing of any patent applications. The Parties agree that the provisions of this Section 4 shall survive the termination or completion of this Agreement as required.

4.2 The SUB INVESTIGATOR and the SUB INSTITUTION agree to acknowledge the Funding Source in all manuscripts, presentations, and abstracts published in accordance with the terms of this Agreement.

4.3 Acknowledgment. The SUB INVESTIGATOR and the SUB INSTITUTION agree that any manuscripts, presentations, and abstracts (including, without limitation, news releases, articles, brochures, advertisements, still and motion pictures, speeches, trade association meetings, and symposia) published in accordance with the terms of this Agreement will included the statements below, as applicable:

(1) "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office";

(2) "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Peer Reviewed Orthopedic Research Program under Award No. W81XWH-17-1-0665. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."

(3) "In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture."

(4) "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules."

(5) "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories."

4.4 Public release. Prior to release to the public, SUB INVESTIGATOR and the SUB INSTITUTION agree to notify PRINCIPAL INVESTIGATOR AND PRINCIPAL INSTITUTION of the following: planned news releases, planned publicity, advertising material concerning project work, and planned presentations to scientific meetings. This provision is not intended to restrict dissemination of research information, but to inform PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION of planned release of information in order to adequately respond to inquiries and to be alert to the possibility of inadvertent release of information which could be taken out of context.

4.5 Failure to include the above statements and adhere to the above regulations, when required, may result in termination of this Agreement.

5. Confidentiality

5.1 Except as otherwise permitted pursuant to this Agreement, the SUB INVESTIGATOR and the SUB INSTITUTION may not disclose to any third party either the terms of this Agreement or any information disclosed to it under or in conjunction with this Agreement that is information of a confidential nature (collectively "Confidential Information") for a period of five (5) years from the later of, the date of disclosure or the termination date of the Clinical Study. However, the SUB INVESTIGATOR and the SUB INSTITUTION may disclose Confidential Information to employees necessary for the conduct of the Clinical Study or to appropriate management personnel responsible for their operations and who are subject to similar obligations of confidentiality. This non-disclosure obligation shall not apply to: (a) information that is in the public domain or subsequently enters the public domain through no fault of a Party to this Agreement; (b) information that is presently known or becomes known to a Party to this Agreement from their own independent sources, from a person having the legal right to disclose such information; (c) information that is independently developed by a Party to this Agreement, as evidenced by that Party's written records; (d) information received by a party to this Agreement from any third party who, to the knowledge of receiving Party, is not under a confidential obligation to keep such information confidential; (e) information that is required to be disclosed by law; (f) information that is required to answer a patient's reasonable questions during the informed consent process; (g) information that is required to be disclosed to obtain ethical and administrative approval for the Clinical Study; or (h) information that is reasonably required for the medical treatment or counseling of Participants.

5.2 If the SUB INVESTIGATOR and/or the SUB INSTITUTION is required to disclose Confidential Information pursuant to Section 5.1(e), such Party shall, unless prohibited by law from doing so, notify the PRINCIPAL INSTITUTION and the

Parties shall agree to a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law.

5.3 Data generated by this Clinical Study will be considered the Confidential Information of the PRINCIPAL INVESTIGATOR, and may not be disclosed except to the extent that it is included in a publication, pursuant to Section 4 of this Agreement.

5.4 The SUB INSTITUTION and the SUB INVESTIGATOR agree to return to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION, as applicable and upon request, the materials, samples, graphics, writings, and information in other tangible forms, containing any Confidential Information provided by such Parties, and all copies of such Confidential Information, excepting one (1) archival copy to be retained by the SUB INSTITUTION and SUB INVESTIGATOR's legal records for purposes of observing compliance with this Agreement, and excepting all medical records reasonably required and all source documents. As per Health Canada regulations, SUB INSTITUTION and/or SUB INVESTIGATOR must retain all documents related to this Clinical Study for 25 years after the study closes

5.5 No license, express or implied, to use the Confidential Information is granted to the SUB INSTITUTION or the SUB INVESTIGATOR other than to use the Confidential Information in the manner and to the limited extent authorized by this Agreement.

6. Patient Confidentiality

All Parties shall (a) comply with applicable health information and privacy legislation, including without limitation, the *Personal Information Protection and Electronic Documents Act*, S.C. 2000, c. 5, the *Health Information Act* (Alberta); (b) comply with any reasonable conditions and requirements imposed by SUB INSTITUTION or SUB INVESTIGATOR (together, the "Custodian") relating to the use, protection, disclosure, return or disposal of any Participant's individually identifying health information ("Health Information") or relating to safeguards against the identification, direct or indirect, of any Participants; (c) use Health Information only for the purpose of conducting the Clinical Study; (d) not publish the Health Information in a form that could reasonably enable the identity of an individual who is the subject of the information to be readily ascertained; (e) not make any attempt to contact any Participants to obtain additional Health Information unless the Participant has provided Custodian with consent regarding the same; (f) be liable for the actions of its employees, agents, consultants or other persons for whom they are in law responsible respecting the collection, use or disclosure of Health Information and for ensuring compliance with applicable legislation by these persons; and (g) ensure that Health Information will not be disclosed to any third parties, except where such disclosure is required by law. The specific data elements being provided are identified in Attachment D (Data Elements) attached hereto and forming a part of this Agreement.

7. Intellectual Property

7.1 Nothing contained in this Agreement shall be deemed to grant any right to any inventions, ideas, discoveries, innovations, devices, data, mechanisms, substances, technologies, works, trade secrets, know-how, formulae and methods, including improvements, whether or not protectable by patent, copyright or other intellectual property rights (collectively "IP") of any Party to this Agreement.

7.2 Notwithstanding Section 7.1, all IP made or conceived by the SUB INSTITUTION or the SUB INVESTIGATOR in the performance of the Clinical Study is the sole and exclusive property of the PRINCIPAL INSTITUTION, PRINCIPAL INSTITUTION grants the SUB INSTITUTION and SUB INVESTIGATOR a royalty-free license to use any such IP and any data generated from the Clinical Study for its/his/her internal educational, non-commercial research and patient care purposes in compliance with any applicable laws and regulations.

8. Indemnity and Insurance

8.1 Each Party agrees to be responsible for any and all claims, demands, actions and costs whatsoever to the extent that may arise, directly or indirectly, out of its/his/her (including its/his/her officers, directors and employees (a) violation of any law or regulation; (b) breach of this Agreement; or (c) negligent or wrongful act or omission. PRINCIPAL INSTITUTION shall at its sole cost and expense, procure and maintain comprehensive general liability insurance coverage in the amounts not less than five million Canadian dollars ($5,000,000 CAD) per incident and five million Canadian dollars ($5,000,000 CAD) annual aggregate. Such comprehensive general liability insurance shall provide: (i) clinical trial liability coverage and (ii) broad form contractual liability coverage for the Party's indemnification obligations under this Agreement. The UNIVERSITY agrees to maintain comprehensive general liability and educational errors and omissions liability insurance, with minimum amounts of $5,000,000 per occurrence and $5,000,000 in the aggregate. AHS agrees to maintain liability protective coverage for bodily injury, property damage and errors and omissions insurance with minimum amounts of $5,000,000 per occurrence and $5,000,000 in the aggregate. The minimum amounts of insurance coverage required under this Section 8.1 shall not be construed to create a limit of a Party's liability with respect to its obligation under this Agreement.

8.2 PRINCIPAL INVESTIGATOR and SUB INVESTIGATOR shall maintain his/her membership in the Canadian Medical Protective Association throughout the term of this Agreement.

8.3 The PRINCIPAL INSTITUTION shall provide the other Parties with written evidence of such insurance upon request from the other Parties. Additionally, a Party shall provide the other Parties with written notice at least fifteen (15) days prior to the cancellation, non-renewal or material change in such insurance.

8.4 The manufacturer of the Study Drug and placebo has agreed to provide an indemnity to participating sites for any third party claims arising from the negligence or wilful misconduct of the manufacturer in connection with the manufacturing and distribution of the Study Drug and placebo.

9. Termination

9.1 The terms of this Agreement shall commence on the Effective Date and shall remain in effect until the completion of the Clinical Study, unless otherwise extended, renewed, amended or earlier terminated in accordance with the provisions of this Agreement.

9.2 If any Party is in default of any of the terms of this Agreement and if thirty (30) days after written notice of default has been given to the defaulting Party the defaulting Party has not taken immediate action to correct such default, any of the non-defaulting Parties may terminate this Agreement immediately.

9.3 If any Party to this Agreement has a significant concern for the safety of patients participating in the Clinical Study, that Party may suspend or terminate this Agreement. The Party that invokes this provision shall provide prompt notice in writing to the other Parties.

9.4 In the event that the SUB INVESTIGATOR is unable to complete the Clinical Study or ceases his/her participation in the Clinical Study, the SUB INVESTIGATOR and/or SUB INSTITUTION will promptly provide written notice to the PRINCIPAL INVESTIGATOR and PRINCIPAL INSTITUTION and will make reasonable efforts to find another SUB INVESTIGATOR acceptable to the PRINCIPAL INVESTIGATOR and the PRINCIPAL INSTITUTION. In the event that no acceptable substitute investigator can be found, this Agreement will terminate.

9.5 SUB INSTITUTION and/or SUBINVESTIGATOR may terminate this Agreement immediately upon written notice to PRINCIPAL INSTITUTION and PRINCIPAL INVESTIGATOR if the approval of the Funding Source is withdrawn or if funds are no longer available for the continuation of the Study.

9.6 Any Party may terminate this Agreement at any time on thirty (30) days written notice to the other Parties.

9.7 Termination of this Agreement will not affect the validity of any provisions that are, expressly or by implication, to survive or to take effect after such termination.

9.8 Immediately upon receipt of notice of termination of the Agreement, if applicable, the SUB INVESTIGATOR and SUB INSTITUTION shall stop enrolling Participants into the Clinical Study and shall cease conducting procedures on the Participants already entered in the Clinical Study as directed by the PRINCIPAL INVESTIGATOR and to the extent medically permissible.

9.9 Upon receipt of notice of termination of the Agreement, the SUB INVESTIGATOR and SUB INSTITUTION shall use their best efforts to promptly limit or terminate any outstanding commitments and Clinical Study related expenses.

9.10 In the event of early termination of this Agreement, upon receipt of approved invoices by the PRINCIPAL INVESTIGATOR, PRINCIPAL INSTITUTION shall pay the SUB INSTITUTION in accordance with the Payments in ATTACHMENT C for all completed services related to the Clinical Study up to the effective date of termination of the Agreement and the SUB INSTITUTION's committed and reasonable non-cancellable costs. If applicable, SUB INSTITUTION shall return any unearned Payments advanced to the SUB INSTITUTION by the PRINCIPAL INSTITUTION.

10. Notices

10.1 Any notice, request, demand or communication required or permitted to be given or made hereunder shall be in writing and shall be well and sufficiently given or made if:

(a) delivered in person or by courier during normal business hours on a business day and left with the addressee or a receptionist or other responsible employee at the relevant addresses or;

(b) sent by fax or other means of recorded electronic communication;

to the SUB INVESTIGATOR:

Dr. Robert Chan
c/o Anelise Silveira
6-110 Clinical Sciences Building
11306 83 Avenue Northwest, University of Alberta,
Edmonton, Alberta, Canada T6G 2G3
Phone: 780-569-5494
Email: anelise.silveira@albertahealthservices.ca

to the SUB INSTITUTION:

Alberta Health Services and
The Governors of the University of Alberta
Suite 400, 8215 – 112 Street
Edmonton, Alberta, Canada T6G 2C8
Attn: Director of Operations
Phone: 780.407.8007
Email: ron.welch@ahs.ca

to the PRINCIPAL INVESTIGATOR:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z6
Canada

to the PRINCIPAL INSTITUTION:

The Governors of the University of Calgary

Legal, Research Services - CSM

Office G360, Ground Floor Health Sciences Building

3280 Hospital Drive NW

Calgary, Alberta, Canada T2N 4Z6

Attn: Manager

Tel: (403) 210-7813

10.2 Any notice or other communications given in compliance with Section 10.1 or made shall be deemed to have been given or made on the same day and to have been received on the day of delivery if delivered as foresaid or on the day of faxing or sending of the same by other recorded means of an electronic communications provided such day is a business day and if not on the first business day thereafter. Any Party to this Agreement may from time to time change the address for notice by notice to the other Parties.

11. Independent Contractor

The relationship between the Parties is that of independent contractors and nothing in this Agreement shall constitute an agency relationship, employment relationship, partnership or a joint-venture between the Parties or any two of them. No Party shall have the authority to act on behalf of any other Party or to bind another Party in any manner.

12. Waiver

No failure or delay by other Party in exercising any right or remedies shall operate as a waiver thereof nor shall any single or partial exercise or waiver of any right or remedy preclude its further exercise or the exercise of any other right or remedy.

13. Applicable Law

This Agreement shall be construed and interpreted in accordance with the laws of the Province of Alberta and the federal laws of Canada applicable therein.

14. Warranties

The Parties make no promises of success in achieving any particular result. Except as expressly provided in this Agreement, no Party gives representation or warranty whatsoever, express or implied, as to any matter, including, without limitation, as to the results of the Clinical Study or regarding Confidential Information that a Party may disclose to another party. No Party will be responsible for any lost profits, lost opportunities, or other indirect or consequential damages suffered by any other party as a result of the conduct of the Clinical Study or the performance of this Agreement.

15. Entire Agreement, Amendment and Assignment

15.1 This Agreement including the attachments attached hereto shall be incorporated herein as part of this Agreement. This Agreement supersedes all prior negotiations and agreements, contains the entire understanding between the Parties hereto regarding the subject matter of this Agreement and may be modified only by further written agreement and signed by all Parties or their authorized representatives.

15.2 No part of this Agreement may be assigned or subcontracted by any Party to any other person or third party without the prior written approval of the other Parties.

16. Severability

Any provision hereof that is prohibited or unenforceable in any jurisdiction will, as to such jurisdiction, be ineffective to the extent of such prohibition or unenforceability without invalidating the remaining provisions hereof, and any such prohibition or unenforceability in any jurisdiction will not invalidate or render unenforceable such provision in any other jurisdiction.

17. Headings

The headings herein are inserted for convenience of reference only and shall not be used in interpreting or construing this Agreement.

18. Enurement

This Agreement shall enure to and be binding upon the Parties hereto and their respective successors and permitted assigns.

19. Survival

The terms of provisions, covenants and conditions contained in this Agreement which by the terms hereof require their performance by the Parties hereto after the completion or termination of this Agreement shall be and remain in force notwithstanding such completion or other termination of this Agreement for any reason whatsoever. Specifically, the following Sections will survive completion or termination of this Agreement: 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 13, 14, and 16.

20. Separate Obligations

The obligations, liabilities, covenants, certifications, warranties and representations hereunder of AHS, University and SUB INVESTIGATOR are several, not joint, and are entered into by each party separately, only in respect of such party and not in respect of, or on behalf of, any other party.

21. Force Majeure

If the performance of this Agreement is prevented, restricted, interfered with or delayed, (either totally or in part) by reason of any cause beyond the reasonable control of the Parties (such as acts of God, explosion, disease, weather, war, terrorism, insurrection, civil strike, riots or power failure), the Party so affected shall, upon giving written notice to the other Party, be excused from such performance to the extent of such prevention, restriction, interference or delay, provided that the affected Party shall use its reasonable efforts to avoid or remove such causes of non-performance and shall continue performance with the utmost dispatch whenever such causes are removed

22. Counterparts

This Agreement may be executed in two or more counterparts, which may be delivered by electronic mail in "portable document format" ('.pdf' format), each of which shall be deemed to be an original and all of which shall together be deemed to constitute one agreement.

The remainder of this page is intentionally left blank.

Signature page follows

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

PRINCIPAL INVESTIGATOR:

Signature: _____ March 13, 2019

Dr. Kevin Hildebrand — Date

PRINCIPAL INSTITUTION:

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Per: _____ MAR 0 5 2019

Marcello Tonelli — Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: Robert Koon Wah Chan Feb 11, 2019

Robert Koon Wah Chan (AKA Robert Chan) — Date

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized

Signatures: _____ _____

Dr. David Williams — Date

Academic Department Chair

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: _____ MAR 0 5 2019

Marcello Tonelli Date

Senior Associate Dean, Health Research

SUB INVESTIGATOR:

Signature: Robert K W Chan _____ Feb 11, 2019

Robert Koon Wah Chan (AKA Robert Chan) Date

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized

Signatures: _____ _____

Dr. David Williams Date

Academic Department Chair

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: _____ _____

Robert Koon Wah Chan (AKA Robert Chan) Date

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized Signatures: _____ February 11, 2019

Dr. David Williams Date

Academic Department Chair

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized
Signatures: _____ FEB 11 2019

Julaine Herst
Research Services Office

Date

Julaine Herst
Assistant Director, Contracts & Agreements
RESEARCH SERVICES OFFICE
The University of Alberta

SUB INSTITUTION:

Alberta Health Services

Authorized
Signatures: _____ _____

Ronald Welch
Research Administration

Date

SUB INSTITUTION:

Alberta Health Services

Authorized
Signatures: _____ _____

Chris Wing
Finance and Administration

Date

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized

Signatures: _____ _____

Julaine Herst
Research Services Office

Date

SUB INSTITUTION:

Alberta Health Services

Authorized

Signatures: _____ 4 May 2017

Ronald Welch
Research Administration

Date

SUB INSTITUTION:

Alberta Health Services

Authorized

Signatures: _____ _____

Chris Wing
Finance and Administration

Date

SUB INSTITUTION:

The Governors of the University of Alberta

Authorized

Signatures: _____ _____

Julaine Herst
Research Services Office

Date

SUB INSTITUTION:

Alberta Health Services

Authorized

Signatures: _____ _____

Ronald Welch
Research Administration

Date

SUB INSTITUTION:

Alberta Health Services

Authorized

Signatures: March 1/2019

Chris Wing
Finance and Administration

Date

ATTACHMENT A

(Prime Agreement)

(Attached hereto)

ATTACHMENT B

(Protocol)

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)

(Previously provided and incorporated herein by reference)

ATTACHMENT C

(Site Budget)

Budget Breakdown/ Payment Schedule:

All payments are fee for service, invoice based

Payment Schedule:

Year 1-2019

Payments to be made Quarterly	Description		Description		Description		Description		Year 1 Total
	Study Coordinator	Indirect (69.0%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
June 30, 2019-	1,815.00	1252.35	180.00	0	30.00	0	2,640.00	0	
September 30, 2019-	3,170.00	2187.3	360.00	0	70.00	0	120.00	0	
December 30, 2019-	3,420.00	2359.8	400.00	0	80.00	0	120.00	0	
TOTAL	**8,405.00**	**5,799.45**	**940.00**	**0.00**	**180.00**	**0.00**	**2,880.00**	**0.00**	**18,204.45**

Year 2-2020

Payments to be made Quarterly	Description		Description		Description		Description		Year 2 Total
	Study Coordinator	Indirect (69.0%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2020-	4,025.00	2777.25	460.00	0.00	90.00	0.00	1200.00	0.00	
June 30, 2020-	5,025.00	3467.25	620.00	0.00	130.00	0.00	150.00	0.00	
September 30, 2020-	5,275.00	3639.75	660.00	0.00	140.00	0.00	150.00	0.00	
December 30, 2020-	4,670.00	3222.3	600.00	0.00	130.00	0.00	120.00	0.00	
TOTAL	**18,995.00**	**13,106.55**	**2,340.00**	**0.00**	**490.00**	**0.00**	**1,620.00**	**0.00**	**36,551.55**

Year 3-2021

Payments to be made Quarterly	Description		Description		Description		Description		Year 3 Total
	Study coordinator	Indirect (69.0%)	Parking	Indirect (NA)	Beverage	Indirect (NA)	Pharmacy	Indirect (NA)	
March 30, 2021-	2,250.00	1552.5	360.00	0.00	90.00	0.00	1050.00	0.00	
June 30, 2021-	1,250.00	862.5	200.00	0.00	50.00	0.00	0.00	0.00	
September 30, 2021-	1,250.00	862.5	200.00	0.00	50.00	0.00	0.00	0.00	
December 30, 2021-	1,000.00	690	160.00	0.00	40.00	0.00	1,500.00	0.00	
TOTAL	**5,750.00**	**3,967.50**	**920.00**	**0.00**	**230.00**	**0.00**	**2,550.00**	**0.00**	**13,417.50**

TOTAL BUDGET: $68,173.50 CAD which includes Study Coordinator time, Participant parking and Food/Beverage cards, and Pharmacy fees. All payments are fee for service on a per participant basis, invoice based.

68,173.50

The Table below outlines the components of the per participant payments used in the subsequent budget calculations.

The per participant Payment of C$1,275 is broken down into study milestone and cost type as follows:

Milestone	*Study coordinator*	*Parking*	*Beverage/Food card*	*Total*
Enrollment	$605	$60	$10	$675
12 weeks	$250	$40	$10	$300
52 Weeks	$250	$40	$10	$300
Total	$1,105	$140	$30	$1,275

B. OTHER PERSONNEL

Study Coordinator:

Year 2019:	Q2	Enrollment - 3 participants x $605/participant =	$1,815
			C$1,815
	Q3	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 3 participants x $250/participant =	$750
			C$3,170
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 4 participants x $250/participant =	$1,000
			C$3,420
Year 2020:	Q1	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 4 participants x $250/participant =	$1,000
			C$4,025
	Q2	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 3 participants x $250/participant =	$750
			C$5,025
	Q3	Enrollment - 5 participants x $605/participant =	$3,025
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$5,275
	Q4	Enrollment - 4 participants x $605/participant =	$2,420
		12 weeks – 5 participants x $250/participant =	$1,250
		52 weeks – 4 participants x $250/participant =	$1,000
			C$4,670
Year 2021:	Q1	12 weeks - 4 participants x $250/participant =	$1,000
		52 weeks – 5 participants x $250/participant =	$1,250
			C$2,250
	Q2	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q3	52 weeks – 5 participants x $250/participant =	$1,250
			C$1,250
	Q4	52 weeks – 4 participants x $250/participant =	$1,000
			C$1,000

Participant Parking:

Year 2019:	Q2	Enrollment - 3 participants x $60/participant =	$180
			C$180
	Q3	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 3 participants x $40/participant =	$120
			C$360
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 4 participants x $40/participant =	$160
			C$400
Year 2020:	Q1	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 4 participants x $40/participant =	$160
			C$460
	Q2	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 3 participants x $40/participant =	$120
			C$620
	Q3	Enrollment - 5 participants x $60/participant =	$300
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$660
	Q4	Enrollment - 4 participants x $60/participant =	$240
		12 weeks – 5 participants x $40/participant =	$200
		52 weeks – 4 participants x $40/participant =	$160
			C$600
Year 2021:	Q1	12 weeks - 4 participants x $40/participant =	$160
		52 weeks – 5 participants x $40/participant =	$200
			C$360
	Q2	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q3	52 weeks – 5 participants x $40/participant =	$200
			C$200
	Q4	52 weeks – 4 participants x $40/participant =	$160
			C$160

Participant Beverage/Food card:

Year 2019:	Q2	Enrollment - 3 participants x $10/participant =	$30
			C$30
	Q3	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 3 participants x $10/participant =	$30
			C$70
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 4 participants x $10/participant =	$40
			C$80
Year 2020:	Q1	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 4 participants x $10/participant =	$40
			C$90
	Q2	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 3 participants x $10/participant =	$30
			C$130

	Q3	Enrollment - 5 participants x $10/participant =	$50
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$140
	Q4	Enrollment - 4 participants x $10/participant =	$40
		12 weeks – 5 participants x $10/participant =	$50
		52 weeks – 4 participants x $10/participant =	$40
			C$130
Year 2021:	Q1	12 weeks - 4 participants x $10/participant =	$40
		52 weeks – 5 participants x $10/participant =	$50
			C$90
	Q2	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q3	52 weeks – 5 participants x $10/participant =	$50
			C$50
	Q4	52 weeks – 4 participants x $10/participant =	$40
			C$40

Investigational Drug Service

Year 2019:	Q2	Start Up Fee	=	$1,500
		Maintenance Fee -	=	$1,050
		Dispensing fee – 3 participants x $30/participant =		$90
				C$2,640
	Q3	Dispensing fee – 4 participants x $30/participant =		$120
				C$120
	Q4	Dispensing fee – 4 participants x $30/participant =		$120
				C$120
Year 2020:	Q1	Maintenance Fee -	=	$1,050
		Dispensing fee – 5 participants x $30/participant =		$150
				C$1,200
	Q2	Dispensing fee – 5 participants x $30/participant =		$150
				C$150
	Q3	Dispensing fee – 5 participants x $30/participant =		$150
				C$150
	Q4	Dispensing fee – 4 participants x $30/participant =		$120
				C$120
Year 2021:	Q1	Maintenance Fee -	=	$1.050
				C$1,050
	Q2	Maintenance Fee -	=	$0
				C$0
	Q3	Maintenance Fee -	=	$0
				C$0
	Q4	Close-out Fee	=	$1,500
				C$1,500

H. INDIRECT COSTS

1. General & Administrative:

The University of Alberta US Indirect cost agreement rate is 69.0%. All salaries and wages, and fringe benefits are included in the calculation. The participant support costs such as parking and beverage/food cards, and the Investigational Drug Services, are not included.

ATTACHMENT D

Data Elements

Data Set	Description of Personal Health Information to be Disclosed for Research Purposes by AHS.
Data contained in the Research Ethics Board-approved case report forms for the study entitled "PrEvention of posttraumatic contractuRes with Ketotifen II (PERK II)"	

The data elements collected as a part of the Clinical Study and documented in any applicable case report forms or data capture tools to the extent that they exist on the records of patients who have been consented to participate in the Clinical Study, may be disclosed to SUB INVESTIGATOR under Section 54 of the Health Information Act of Alberta after the protocol has been approved by the local Research Ethics Board.

In the transfer of Clinical Study data to the PRINCIPAL INSTITUTION, reasonable efforts should be made, where possible, to de-identify any potentially identifying health information/data elements of Participants in accordance with Alberta Health Services' Non-Identifying Health Information Standard (http://www.albertahealthservices.ca/about/Page210.aspx).

Significant deviation from the data listed above will require an amendment to this agreement.

The following potentially identifying data elements are to be provided to the PRINCIPAL INSTITUTION in accordance with the terms and conditions of this Agreement:

- Date of injury
- Date of surgery (ies)
- Date of discharge
- Adverse event start/end date(s)
- SAE start/end date(s)

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)

Date:	February 7, 2019
Principal Investigator:	Dr. J Whitcomb Pollock, TOH/OHRI
Protocol ID:	20180806-01H
Study Title:	PrEvention of posttraumatic contractuRes with Ketotifen 2
Submission Type:	Initial Application
Review Type:	Full Board
Meeting Date:	November 19, 2018
Date of Approval:	February 7, 2019
Approval Expiry Date:	February 7, 2020

Dear Dr. Pollock,

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

This study is subject to the U.S. code of Federal Regulations; therefore, full board review is required for all continuing review.

The **OHSN-REB ethics approval** is applicable only for The Ottawa Hospital, University of Ottawa Heart Institute and University of Ottawa Faculty of Medicine.

An **Institutional approval (OHRI) letter is required prior to the conduct of the study** at this site. The institutional approval letter is an indication that you have satisfied ethics, contracts, departmental notifications, as applicable.

Documents Approved:

Document Name	Document Version Date
French Participant Diary	May 9, 2018
English DASH	June 27, 2018

Approval Form

Date:	November 21, 2018
Principal Investigator:	Koon Wah Chan
Study ID:	Pro00083891
Study Title:	PrEvention of posttraumatic joint contractuRes with Ketotifen 2
Approval Expiry Date:	November 20, 2019

Date of Informed Consent:	Approval Date	Approved Document
	11/21/2018	SCH ICF_notrackchanges_15NOV18.docx

Funding/Sponsor: United States of America Department of Defense

Thank you for submitting the above study to the Health Research Ethics Board - Biomedical Panel. This application was given a delegated review due to previous review and approval by the University of Calgary CHREB, a member of the Alberta Research Ethics Reciprocity Agreement. Your application has been reviewed and approved on behalf of the committee. The following documentation forms part of this approval:

- Protocol Version 4.0 (31 Jul 2018);
- Product Monograph for Ketotifen Fumarate (15 Aug 2012);
- Main Consent Form Version 4.0 (15 Nov 2018);
- DASH Questionnaire;
- OES Questionnaire;
- PCS User Manual;
- Case Report Forms V1.4;
- Participant Diary;
- Home Exercise Program Guideline;
- Participant Card v1.0 (18 Jul 2018).

We acknowledge receipt of the Health Canada No Objection Letter re: PERK2_KAH Version 3.0 (09 Aug 2018).

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the HREB - Biomedical Panel. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (November 20, 2019), you will have to re-submit an ethics application.

The membership of the Health Research Ethics Board - Biomedical Panel complies with the membership requirements for research ethics boards as defined in Division 5 of the Food and Drug Regulations and the Tri-Council Policy Statement. The HREB - Biomedical Panel carries out its functions in a manner consistent with Good Clinical Practices and the Canadian General Standards Board (CAN/CGSB-101.1-2013).

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Research Administration office, #507 College Plaza, email nactrc.contracts@albertahealthservices.ca.

Sincerely,

Robert P. Rennie, PhD, FCCM, D(ABMM)
Associate Chair, Health Research Ethics Board – Biomedical Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Conjoint Health Research Ethics Board
Research Services Office
2500 University Drive, NW
Calgary AB T2N 1N4
Telephone: (403) 220-2297
chreb@ucalgary.ca

CERTIFICATION OF INSTITUTIONAL ETHICS APPROVAL

The Conjoint Health Research Ethics Board (CHREB), University of Calgary has reviewed and approved the following research protocol:

Ethics ID:	REB18-1228
Principal Investigator:	Prism Schneider
Co-Investigator(s):	Richard Buckley Paul J. Duffy Kevin Hildebrand Robert Korley Jeremy LaMothe Ian Le Christopher Martin Nicholas George H. Mohtadi Tolulope Sajobi Richard Walker
Student Co-Investigator(s):	There are no items to display
Study Title:	PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)
Sponsor:	United States of America Department of Defence

Effective: 31-Jul-2019 **Expires:** 31-Jul-2020

The following documents have been approved for use:

- PERK 2 Poster FMC_April 18, 2019, April 18, 2019
- PERK 2 FMC Consent Form_April 17, 2019_clean, 4.0, April 17, 2019
- PERK 2_CRF_V1.5_clean, 1.5
- PERK 2 Drug Info Sheet_Dec 5, 2018, December 5, 2018
- PERK 2 HEP Guidelines_May 29, 2018, May 29, 2018
- PERK 2 Participant Diary_clean, July 6, 2018

- DASH Questionnaire_2010
- PERK 2 Patient Demographics_Feb 5, 2019, February 5, 2019
- Oxford Elbow Score (OES)_English_2008, June 27, 2018
- PERK 2 Participant Wallet Card, July 18, 2018
- The Pain Catastrophizing Scale (PCS)_English_1995
- PERK 2 Protocol Agreement FMC_Feb 12, 2019, February 12, 2019
- PERK 2 Protocol_V4.0_clean, 4.0, July 31, 2018
- PERK 2 Protocol V3.0_clean, 3.0, July 6, 2018
- Ketotifen Product Monograph, August 15, 2012
- PERK 2 Health Canada No Objection Letter_Aug 9, 2018, August 9, 2018

The CHREB is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS); International Conference on Harmonization E6: Good Clinical Practice Guidelines (ICH-GCP); Part C, Division 5 of the Food and Drug regulations, Part 4 of the Natural Health Product Regulations and the Medical Device Regulations of Health Canada; Alberta's Health Information Act, RSA 2000 cH-5; and US Federal Regulations 45 CFR part 46, 21 CFR part 50 and 56.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

Restrictions:

This Certification is subject to the following conditions:

1. Approval is granted only for the research and purposes described in the application.
2. Any modification to the approved research must be submitted to the CHREB for approval.
3. An annual application for renewal of ethics certification must be submitted and approved by the above expiry date.
4. A closure request must be sent to the CHREB when the research is complete or terminated.

Approval by the REB does not necessarily constitute authorization to initiate the conduct of this research. The Principal Investigator is responsible for ensuring required approvals from other involved organizations (e.g., Alberta Health Services, community organizations, school boards) are obtained.

Approved By:	**Date:**
Kathleen Oberle, PhD, Vice-Chair , CHREB	31-Jul-2019

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Conjoint Health Research Ethics Board
Research Services Office
2500 University Drive, NW
Calgary AB T2N 1N4
Telephone: (403) 220-2297
chreb@ucalgary.ca

CERTIFICATION OF INSTITUTIONAL ETHICS APPROVAL

The Conjoint Health Research Ethics Board (CHREB), University of Calgary has reviewed and approved the following research protocol:

Ethics ID:	REB17-2383
Principal Investigator:	Neil White
Co-Investigator(s):	Eldridge Batuyong Gurpreet Dhaliwal Andrew Dodd Christina Hiscox Stephen Hunt Justin LeBlanc Marlis Sabo
Student Co-Investigator(s):	There are no items to display
Study Title:	Prevention of Post-Traumatic Contracture with Ketotifen 2 (PERK 2)
Sponsor:	United States of America Department of Defense

Effective: Friday, February 22, 2019 **Expires:** Saturday, February 22, 2020

This study has been reviewed by the full Conjoint Health Research Ethics Board of the University of Calgary on October 04, 2018.

The following documents have been approved for use:

- Informed Consent Form (Cleaned), 1.2, February 12, 2019
- Disabilities of the Arm, Shoulder and Hand Questionnaire
- Participant Wallet Card, 1.0, July 18, 2018
- Pain Catastrophizing Scale (Manual & Questionnaire)
- Case Report Forms, 1.4, June 25, 2018
- Participant Home Exercise Program Guidelines, May 29, 2018
- Oxford Elbow Score, June 27, 2018
- Participant Study Medication Diary, 1.0, July 6, 2018
- PERK II Study Protocol, 1.0, September 1, 2018
- Ketotifen Product Monograph , August 15, 2012
- No Objection Letter RE: Protocol #PERK2_KAH (Version 3.0), August 9, 2018

The CHREB is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS); International Conference on Harmonization E6: Good Clinical Practice Guidelines (ICH-GCP); Part C, Division 5 of the Food and Drug regulations, Part 4 of the Natural Health Product Regulations and the Medical Device Regulations of Health Canada; Alberta's Health Information Act, RSA 2000 cH-5; and US Federal Regulations 45 CFR part 46, 21 CFR part 50 and 56.

You and your co-investigators are not members of the CHREB and did not participate in review or voting on this study.

Restrictions:

This Certification is subject to the following conditions:

1. Approval is granted only for the research and purposes described in the application.
2. Any modification to the approved research must be submitted to the CHREB for approval.
3. An annual application for renewal of ethics certification must be submitted and approved by the above expiry date.
4. A closure request must be sent to the CHREB when the research is complete or terminated.

Approval by the REB does not necessarily constitute authorization to initiate the conduct of this research. The Principal Investigator is responsible for ensuring required approvals from other involved organizations (e.g., Alberta Health Services, community organizations, school boards) are obtained.

Approved By:	**Date:**
Stacey A. Page, PhD, Chair , CHREB	Friday, February 22, 2019

Note: This correspondence includes an electronic signature (validation and approval via an online system).

Western Research

Date: 2 October 2019

To: Dr. Graham King

Project ID: 111346

Study Title: PrEvention of posttraumatic contractuRes with Ketotifen II: PERK II

Application Type: HSREB Initial Application

Review Type: Full Board

Full Board Reporting Date: 20/Aug/2019 13:00

Date Approval Issued: 02/Oct/2019 09:57

REB Approval Expiry Date: 02/Oct/2020

Dear Dr. Graham King

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
AE CRF	Other Data Collection Instruments	25/Jun/2018	1.4
Follow up CRF	Paper Survey	25/Jun/2018	1.4
PERK 2 Business sized wallet cards 20180726	Other Participant Material(s)	26/Jul/2018	1
PERK 2 Participant Diary 20180706	Other Data Collection Instruments	06/Jul/2018	1
PERK 2 Protocol 4.0 20180731	Protocol	31/Jul/2018	4
PERKS II LOI VR 4 2019.09.09	Written Consent/Assent	09/Sep/2019	4
Protocol deviation CRF	Other Data Collection Instruments	25/Jun/2018	1.4
Screening CRF	Other Data Collection Instruments	25/Jun/2018	1.4
X-ray CRF	Other Data Collection Instruments	25/Jun/2018	1.4

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Ketotifen Product Monograph rev 20120815	Product Monograph	15/Aug/2012	2
PERK 2 - DMC charter version 1.0 20190623	DSMB/C Charter	22/Jul/2019	1
PERK 2 NOL218219 20180809	NOL/NOA	09/Aug/2018	1

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Research Ethics Office
Telephone: (416) 864-6060 Ext. 2557
Facsimile: (416) 864-6043
E-mail: pateld@smh.ca

July 24, 2019

Dr. Aaron Nauth,
Department of Surgery, Division of Orthopaedics,
St. Michael's Hospital

Dear Dr. Nauth,

Re: REB# 19-034 - PrEvention of posttraumatic joint contractuRes with Ketotifen 2: PERK 2

REB APPROVAL:	**Original Approval Date**	**July 24, 2019**
	Annual/Interval Review Date	**July 24, 2020**

Thank you for your application submitted on February 07, 2019. At the Unity Health Toronto Research Ethics Board (REB) meeting held on February 27, 2019, the above referenced study was discussed and subsequently the views derived from this discussion have been documented and resolved. Please note that no member of the REB associated with this study was present or involved in its deliberation, review or approval.

The REB approves the study as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004. The REB hereby issues approval for the above named study for a period of 12 months from the date of this letter. Continuation beyond that date will require further review of REB approval.

In addition, the following are appropriate and hereby approved:

1. Protocol ver: 4 31-Jul-2018
2. Phone Script for Study Followup ver: 15-Jul-2019
3. Consent Form ver: 5.2 24-Jul-2019

Furthermore, the following documents have been received and are acknowledged:

1. Case Report Form ver: 1.4 04-Jun-2018
2. Master Linking Log ver: 26-Sep-2018
3. Participant Trial Card ver: 1.0 18-Jul-2018
4. Participant Study Medication Diary (received 07-Feb-2019)
5. DASH Questionnaire (received 07-Feb-2019)
6. PCS Questionnaire (received 07-Feb-2019)
7. Oxford Elbow Score (received 07-Feb-2019)
8. Health Canada NOL Control # 218219
9. University of Calgary REB Approval Letter (received 07-Feb-2019)
10. Department of Health and Human Services Approval Letter (received 07-Feb-2019)
11. Product Monograph ver: 15-Aug-2012
12. Trial Management Group Charter ver: 1.0 23-Jun-2019
13. Data Monitoring Committee Charter ver: 1.0 23-Jun-2019
14. Trial Steering Committee Charter ver: 1.0 23-Jun-2019

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB. Please note that shared electronic health systems such as

ConnectingOntario, PRO, RM&R, OLIS, HDIRS, eCHN, DPV, and IAR do not permit access for research purposes.

For all interventional studies, the study sponsor is required to register the study in a publicly accessible registry prior to enrollment of the first study participant. The study sponsor is also required to ensure that the trial record is updated in a timely manner and the summary results are posted within the required timelines.

All institutional approvals **must be** coordinated and approved through the Office of Research Administration (ORA) prior to initiation of this research. If a Clinical Trial Agreement is required, it must be reviewed and approved by the ORA, prior to commencing any study related activities.

All investigational drug product dispensing must be coordinated through Research Pharmacy.

The REB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, and ICH Good Clinical Practice Consolidated Guideline E6, Health Canada Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Product Regulations, and the Medical Devices regulations. Furthermore, all investigational drug trials at Unity Health Toronto are conducted by Qualified Investigators (as defined in the latter document).

With best wishes

☐ David Mazer, MD
Chair, Research Ethics Board

☒ Philip Berger, MD.
Vice Chair, Research Ethics Board

☐ Michael Szego, PhD
Vice Chair, Research Ethics Board

DM/PB/MS/tps

PROVIDENCE HEALTH CARE
Research Institute

UBC-Providence Health Care Research Institute
Office of Research Services
10th Floor Hornby Site - SPH
c/o 1081 Burrard St.
Vancouver, BC V6Z 1Y6
Tel: (604) 806-8567
Fax: (604) 806-8568

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: ANNUAL RENEWAL

PRINCIPAL INVESTIGATOR:	**DEPARTMENT:**	**UBC-PHC REB NUMBER:**
Thomas Goetz	UBC/Medicine, Faculty of/Orthopaedics	H17-03529

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
Providence Health Care	St. Paul's Hospital

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Jeffrey Pike
Parham Daneshvar

SPONSORING AGENCIES:
US Department of Defense - "PrEvention of posttraumatic contractuRes with Ketotifen II (PERK II)"

PROJECT TITLE:
PrEvention of posttraumatic contractuRes with Ketotifen II (PERK II)

EXPIRY DATE OF THIS APPROVAL: July 2, 2020

APPROVAL DATE: July 2, 2019

CERTIFICATION:

1. The membership of the UBC-PHC REB complies with the membership requirements for research ethics boards defined in Part C Division 5 of the Food and Drug Regulations of Canada.
2. The UBC-PHC REB carries out its functions in a manner fully consistent with Good Clinical Practices.
3. The UBC-PHC REB has reviewed and approved the research project named on this Certificate of Approval including any associated consent form and taken the action noted above. This research project is to be conducted by the principal investigator named above at the specified research site(s). This review of the UBC-PHC REB have been documented in writing.

The UBC-PHC Research Ethics Board Chair or Associate Chair, has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal.

Approval of the UBC-Providence Health Care Research Ethics Board by one of the following:
Dr. Kuo-Hsing Kuo, Chair
Dr. Stephen Hoption Cann, Associate Chair
Dr. I. Fedoroff, Associate Chair

University of Maryland, Baltimore
Institutional Review Board (IRB)
Phone: (410) 706-5037
Fax: (410) 706-4189
Email: hrpo@umaryland.edu

APPROVAL OF RESEARCH NOTIFICATION

Date: June 18, 2019

To: Raymond Pensy
RE: HP-00078753
Type of Submission: Initial Review
Type of IRB Review: Full Board

Approval for this project is valid from 6/6/2019 to 6/5/2020

This is to certify that the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) approved the above referenced protocol entitled, "*Prevention of Post-Traumatic Contractures with Ketotifen*".

The IRB made the following determinations regarding this submission:
- Written informed consent is required. Only the valid IRB-approved informed consent form(s) in CICERO can be used.
- A waiver of HIPAA authorization for release of the PHI identified in the CICERO application has been reviewed and approved for recruitment purposes only.

This study is approved to enroll 110 local participants.

This study is approved to enroll 712 worldwide participants.

Below is a list of the documents attached to your application that have been approved:
PERK 2 consent + HIPAA clean 6.13.19.docx
PERK 2 CDI clean consent + HIPAA 6.13.19.docx
Eligibility Checklist for HP-00078753 v4-30-2019-1556644619512
PERK 2 Protocol 4.0 20180731 Clean.pdf
PERK 2 HIPAA new template 3.13.19.docx
Ketotifen Product Monograph rev 20120815 .pdf
PERK 2 Cognitive Debriefing Script UMD (English US).docx
OES_English_US_FINAL 20180627.pdf
DASH_Spanish.pdf
OES_Spanish_US_FINAL 20180702.pdf
PCS_AU1.0 Spanish US.pdf
DASH_questionnaire_2010.pdf
PCS English.pdf
PCSManual2009.pdf
PERK 2 HEP Guidelines 20180529 Clean SPANISH.pdf
UMD PERK 2_CRF_v1.5.pdf
LAR ID Form.pdf
PERK 2 Participant Diary 20180509 Clean SPANISH.pdf

PERK 2 MOD 3 application REB17-0609 CHREB (Apprv. 20180815).pdf
OES_English_US_FINAL 20180627.pdf
PERK 2 ICF 4.0 20180731 Clean Template.docx
PERK 2 MOD 4 REB17-1109 CHREB (Approval 20181213).pdf
Ketotifen Product Monograph rev 20120815 .pdf
PERK 2 MOD 2 application REB17-0609 CHREB (Apprv. 20180710).pdf
PERK 2 MOD 3 REB17-0609 CHREB (Approval 20180815).pdf
PERK 2 Business sized wallet cards 20180817 SPANISH.pdf
PERK 2 Patient Demographics 20190205 Clean.pdf
PERK 2 MOD 2 REB17-0609 CHREB (Apprv. 20180710).pdf
PERK 2 HEP Guidelines Clean 20180529.pdf
OES_Spanish_US_FINAL 20180702.pdf
PERK 2 Calgary CRF Approval.pdf
PERK 2 Cognitive Debriefing Script UMD (English US).docx
PERK 2 Participant Diary 20181128 Clean Updated.xlsx.pdf
PERK 2 MOD 1 REB17-1109 CHREB (Apprv. 20172111).pdf

In conducting this research you are required to follow the requirements listed in the INVESTIGATOR MANUAL. Investigators are reminded that the IRB must be notified of any changes in the study. In addition, the PI is responsible for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(4)(iii)). The PI must also inform the IRB of any new and significant information that may impact a research participants' safety or willingness to continue in the study and any unanticipated problems involving risks to participants or others.

DHHS regulations at 45 CFR 46.109 (e) require that **continuing review** of research be conducted by the IRB at intervals appropriate to the degree of risk and **not less than once per year.** The regulations make **no provision for any grace period extending the conduct of the research beyond 6/5**/2020**.** You will receive continuing review email reminder notices prior to this date; however, it is your responsibility to submit your continuing review report in a timely manner to allow adequate time for substantive and meaningful IRB review and assure that this study is not conducted beyond **6/5/2020**. Investigators should submit continuing review reports in the electronic system at least six weeks prior to this date.

Research activity in which the VA Maryland Healthcare System (VAMHCS) is a recruitment site or in which VA resources (i.e., space, equipment, personnel, funding, data) are otherwise involved, must also be approved by the VAMHCS Research and Development Committee prior to initiation at the VAMHCS. Contact the VA Research Office at 410-605-7000 ext. 6568 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

If you have any questions about this review or questions, concerns, and/or suggestions regarding the Human Research Protection Program (HRPP), please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@umaryland.edu.

The UNIVERSITY of VERMONT
Committees on Human Subjects
Serving the University of Vermont
and the UVM Medical Center

RESEARCH PROTECTIONS OFFICE
213 Waterman Building
85 South Prospect Street
Burlington, Vermont 05405
(802)656-5040 ph
www.uvm.edu/rpo/

Approval

To:	Michel Benoit
Date:	July 8, 2019
Study#:	19-0049
Study Title:	PrEvention of Posttraumatic Joint ContractuRes with Ketotifen 2 (PERK 2)
Sponsor:	University of Calgary; US Department of Defense/DOD
Finalized Documents:	19-0049_DOD_RequiresLocalIRBApprovalFirst_24May2019.pdf ; 19-0049_PERK_2_DataPlan_19Dec2018.pdf ; Adverse event (J Am Medical Assoc via CSL)_Hildebrand.docx ; DASH_questionnaire_2010.pdf ; IND Approval 20171115.pdf ; Ketotifen Product Monograph rev 20120815 .pdf ; OES_English_US_FINAL 20180627.pdf ; PCS English1995.pdf ; PERK 2 HEP Guidelines Clean 20180529.pdf ; PERK 2 Participant Diary 20180706.pdf ; PERK 2 Protocol 3.0 Clean 20180629.pdf ; UVM_Benoit_PERK 2_Consent_A4_29May2019.pdf ;

This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts; and, when applicable, with the requirements of 21 CFR 50 and 21 CFR 56.

Review Type: Committee

Date of Approval 12/11/2018 Date of expiration 11/20/2019

Effective Date 6/21/2019

Special Determinations:
None
Consent/HIPAA/Waiver Determinations:
Written Consent with Authorization under 46.116, 46.164.508(a)(1)(b)(3)(c)

University of Vermont and State Agricultural College: FWA 00000723 Expiration Date: March 14, 2024
The UVM Medical Center: FWA 00000727 Expiration Date: March 14, 2024
IRB number 00000485

Institutional Signature:
Name and Title of Official: David A. Kaminsky, M.D., Chair

Alexandra Garven

From: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) <kimberly.l.odam.civ@mail.mil>
Sent: Thursday, June 06, 2019 2:08 PM
To: 'kwrchan@gmail.com'
Cc: hildebrk@ucalgary.ca; Alexandra Garven; 'robin.smith@ucalgary.ca'; Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Kiwanuka, Jacqueline N CTR USARMY MEDCOM USAMRMC (USA); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.b2 HRPO Approval Memorandum (Proposal Log Number OR160026, Award Number W81XWH-17-1-0665)

Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

SUBJECT: Initial Approval for the Protocol, “Prevention of Post-Traumatic Contractures With Ketotifen 2,” Submitted by Robert Chan, MD, Sturgeon Community Hospital, St. Albert, Alberta, 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, Alberta, Canada, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.b2 (Sturgeon Community Hospital)

1. The subject protocol (version 4.0 /dated 31 July 2018) was initially approved by the Conjoint Health Research Ethics Board Institutional Review Board (IRB) on 11 September 2017, continued on 11 September 2018, and initially approved following a delegated review by the Alberta Health Research Ethics Board on 21 November 2018 and subsequently on 27 March 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 adult participants with isolated elbow fractures or dislocations from the Sturgeon Community Hospital.

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 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 20 November 2019. 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-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 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 Jacqueline N. Kiwanuka, MBA, Human Subjects Protection Scientist, at 301-619-9267, DSN 343-9267, or jacqueline.n.kiwanuka.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

KIMBERLY L. ODAM, MS, CIP
Acting Director
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.

Alexandra Garven

From: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) <kimberly.l.odam.civ@mail.mil>
Sent: Monday, December 17, 2018 6:48 AM
To: 'michael.bosse@carolinashealthcare.org'
Cc: hildebrk@ucalgary.ca; Alexandra Garven; 'very@ucalgary.ca'; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US); Yadav, Prem CIV USARMY MEDCOM CDMRP (US); Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Roberson, Tykisha L CTR USARMY MEDCOM USAMRMC (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA); Kiwanuka, Jacqueline N CTR USARMY MEDCOM USAMRMC (US)
Subject: A-20465.c, HRPO Approval Memorandum (Proposal Log Number OR160026 Award Number W81XWH-17-1-066)

SUBJECT: Initial Approval for the Protocol, "Prevention of Post-Traumatic Contractures With Ketotifen 2 (PERK 2)," Submitted by Michael J. Bosse, MD Carolinas Healthcare System, Charlotte, North Carolina, in Support of the Proposal, "Prevention of Post-Traumatic Contractures With Ketotifen II (PERK II)," Submitted by Kevin A. Hildebrand, MD, University of Calgary, Calgary, Alberta, Canada, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.c (Carolinas Healthcare System)

1. The subject protocol (version 4.0/dated 31 July 2018) was approved by the Advarra Institutional Review Board (IRB) on 14 September 2018. The Carolinas Healthcare System is relying on the review provided by the Advarra IRB. The U.S. Army Medical Research and Materiel Command (USAMRMC), 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 USAMRMC human subjects protection requirements.

2. The USAMRMC ORP HRPO approved this greater than minimal risk study for the enrollment of 100 adults from the Carolinas Healthcare System.

3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC 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 USAMRMC 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 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 14 September 2019. 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-usamrmc.other.hrpo@mail.mil), by facsimile (301-619-7803), or mail to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-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 USAMRMC 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 USAMRMC 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 USAMRMC 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 Jacqueline N. Kiwanuka, MBA, Human Subjects Protection Scientist, at 301-619-9267, DSN 343-9267, or jacqueline.n.kiwanuka.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight Raquel Jarrett, MPH, Human Subjects Protection Scientist, at extension 301-619- 2380, DSN 343- 2380 or raquel.t.jarrett.ctr@mail.mil

KIMBERLY L. ODAM, MS, CIP
Human Subjects Protection Scientist
Human Research Protection Office
Office of Research Protections
U.S. Army Medical Research and Materiel 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.

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA) <jessica.l.mendoza19.civ@mail.mil>
Sent: Monday, September 16, 2019 8:05 AM
To: 'prism.schneider@gmail.com'
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); 'Alexandra.Garven@albertahealthservices.ca'; Robin Smith; Kevin A. Hildebrand; Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Gerardo Duque; Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA); Anoumatacky-Akesse Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.g - HRPO Approval Memorandum (IRB Study Number 18-1228, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, “Prevention of Post-Traumatic Contractures With Ketotifen 2 (PERK 2),” Submitted by Prism S. Schneider, MD, PhD, University of Calgary - Foothills Medical Centre, Calgary, Alberta, 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, IRB Study Number 18-1228, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.g

1. The subject protocol version 4.0, dated 31 July 2018 was approved by the University of Calgary Conjoint Health Research Ethics Board on 31 July 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 120 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 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 31 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 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-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 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 Ismael Anoumatacky-Akesse Pokou, DDS, Human Subjects Protection Scientist, at 301-619-3190, DSN 343-3190, or namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

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

Alexandra Garven

From: Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US) <kimberly.l.odam.civ@mail.mil>
Sent: Thursday, June 06, 2019 6:30 AM
To: 'neiljwhite@gmail.com'
Cc: hildebrk@ucalgary.ca; Alexandra Garven; 'robin.smith@ucalgary.ca'; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (US); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA); Kiwanuka, Jacqueline N CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.a2 HRPO Approval Memorandum (Proposal Log Number OR160026, Award Number W81XWH-17-1-0665)

Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

SUBJECT: Initial Approval for the Protocol, “Prevention of Post-Traumatic Contractures With Ketotifen 2 (PERK 2),” Submitted by Neil J. White, MD, FRCS(C), South Health Campus Hospital - University of Calgary, Calgary, Alberta, 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, Alberta, Canada, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.a2 (South Health Campus Hospital - University of Calgary)

1. The subject protocol (version 4.0/dated 31 July 2018) was initially approved by the Conjoint Health Research Ethics Board (CHREB), University of Calgary Institutional Review Board (IRB) on 22 February 2019 and subsequently on 29 May 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 70 adult participants with isolated elbow fractures or dislocations from the South Health Campus Hospital – University of Calgary.

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 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 22 February 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-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 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 Jacqueline N. Kiwanuka, MBA, Human Subjects Protection Scientist, at 301-619-9267, DSN 343-9267, or jacqueline.n.kiwanuka.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

KIMBERLY L. ODAM, MS, CIP
Acting Director, Office of Research Protections
Acting Director, Human Research Protection Office
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.

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA) <jessica.l.mendoza19.civ@mail.mil>
Sent: Monday, September 30, 2019 10:10 AM
To: 'nautha@smh.ca'
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Lorna Very; Gerardo Duque; Robin Smith; Kevin A. Hildebrand; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (USA); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA); Anoumatacky-Akesse Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.i - HRPO Approval Memorandum (REB Study Number 19-034, 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 Aaron Nauth, MD, MSc, St. Michael’s Hospital, Toronto, 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, REB Study Number 19-034, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.i

1. The subject protocol version 4.0, dated 31 July 2018 was approved by the Unity Health Toronto Research Ethics Board (REB) on 24 July 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 25 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 24 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-Akesse Pokou, DDS, Human Subjects Protection Scientist, at 301-619-3190, DSN 343-3190, or namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

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

Gerardo Duque

From: Kevin A. Hildebrand
Sent: Monday, September 16, 2019 7:32 AM
To: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)
Cc: Gerardo Duque
Subject: Re: A-20465.d1 and A-20465.1d2 – LIMITED HRPO Approval Memorandum (IRB Study Number 20180806, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

Hi Jessica,

Thanks for the approval notice! In the future can you replace Alexandra Garven with Gerry Duque as he is now in my research coordinator position. I've cc'd Gerry here.

Kevin Hildebrand

From: "Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)" <jessica.l.mendoza19.civ@mail.mil>
Date: Monday, September 16, 2019 at 7:18 AM
To: "'jpollock@toh.ca'" <jpollock@toh.ca>
Cc: "Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US)" <jodi.h.bennett.civ@mail.mil>, "'spapp@toh.ca'" <spapp@toh.ca>, "'Alexandra.Garven@albertahealthservices.ca'" <Alexandra.Garven@albertahealthservices.ca>, Robin Smith <robin.smith@ucalgary.ca>, Kevin Hildebrand <hildebrk@ucalgary.ca>, "Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US)" <kenneth.e.grenier2.civ@mail.mil>, "Yadav, Prem CIV USARMY MEDCOM CDMRP (USA)" <prem.yadav.civ@mail.mil>, "Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA)" <karen.m.eaton.ctr@mail.mil>, "'very@ucalgary.ac'" <very@ucalgary.ac>, "'kmcilquham@ohri.ca'" <kmcilquham@ohri.ca>, "Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA)" <kimberly.l.odam.civ@mail.mil>, "Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)" <jessica.l.mendoza19.civ@mail.mil>, "Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA)" <raquel.t.jarrett.ctr@mail.mil>, "Anoumatacky-Akesse Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)" <namkpri.i.anoumatacky-akessepokou.ctr@mail.mil>
Subject: A-20465.d1 and A-20465.1d2 – LIMITED HRPO Approval Memorandum (IRB Study Number 20180806, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: LIMITED Initial Approval for the Protocol, "Prevention of Post-Traumatic Contractures With Ketotifen 2," Submitted by J. Whitcomb Pollock, MD, The University of Ottawa, Ottawa Hospital – General Campus (TOH-GC), and Steven R. Papp, MD, MSc, The Ottawa Hospital – Civic Campus (TOH-CC), Ottawa, 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, IRB Study Number 20180806, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Numbers A-20465.d1 (TOH-GC Site) and A-20465.d2 (TOH-CC Site)

1. The subject protocol version 4.0, dated 31 July 2018, was approved by the Ottawa Health Science Network (OHSN) Research Ethics Board (REB) on 7 February 2019. The TOH-CC is relying on the review provided by the OHSN REB. 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 60 subjects with the following limitation: Enrollment cannot begin at the TOH-CC site until the HRPO approves the amendment to include the performance site information in the informed consent document.

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 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 7 February 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-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 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 Ismael Anoumatacky-Akesse Pokou, DDS, Human Subjects Protection Scientist, at 301-619-3190, DSN 343-3190, or namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

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

Gerardo Duque

From: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA) <jessica.l.mendoza19.civ@mail.mil>
Sent: Tuesday, September 17, 2019 1:09 PM
To: 'Rpensy@umoa.umm.edu'; 'rpensy@som.umaryland.edu'
Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Gerardo Duque; Robin Smith; Lorna Very; Kevin A. Hildebrand; Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US); Yadav, Prem CIV USARMY MEDCOM CDMRP (USA); Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA); Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA); Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA); Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA); Anoumatacky-Akesse Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)
Subject: A-20465.f - HRPO Approval Memorandum (IRB Study Number 00078753, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, “Prevention of Post-Traumatic Contractures With Ketotifen,” Submitted by Raymond A. Pensy, MD, University of Maryland Medical Center, Baltimore, Maryland, 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, IRB Study Number 00078753, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.f

1. The subject protocol version 4.0, dated 31 July 2018 was approved by the University of Maryland at Baltimore Institutional Review Board (IRB) on 6 June 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 screening 300 volunteers for the enrollment of 110 subjects at the R. Adams Cowley Shock Trauma Center, Midtown Campus and Rehabilitation & Orthopaedic Institute locations.

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 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 5 June 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-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 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 Ismael Anoumatacky-Akesse Pokou, DDS, Human Subjects Protection Scientist, at 301-619-3190, DSN 343-3190, or namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

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

Gerardo Duque

From: Kevin A. Hildebrand
Sent: Monday, September 16, 2019 7:55 AM
To: Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)
Cc: Gerardo Duque
Subject: Re: A-20465.e - HRPO Approval Memorandum (IRB Study Number 19-0049, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

Thanks Jessica.

Kevin Hildebrand

From: "Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)" <jessica.l.mendoza19.civ@mail.mil>
Date: Monday, September 16, 2019 at 7:52 AM
To: "'Michael.Benoit@uvmhealth.org'" <Michael.Benoit@uvmhealth.org>
Cc: "Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US)" <jodi.h.bennett.civ@mail.mil>, Robin Smith <robin.smith@ucalgary.ca>, "'Alexandra.Garven@albertahealthservices.ca'" <Alexandra.Garven@albertahealthservices.ca>, Lorna Very <very@ucalgary.ca>, Kevin Hildebrand <hildebrk@ucalgary.ca>, "Grenier, Kenneth E CIV USARMY MEDCOM USAMRAA (US)" <kenneth.e.grenier2.civ@mail.mil>, "Yadav, Prem CIV USARMY MEDCOM CDMRP (USA)" <prem.yadav.civ@mail.mil>, "Eaton, Karen M CTR USARMY MEDCOM USAMRMC (USA)" <karen.m.eaton.ctr@mail.mil>, "Odam, Kimberly L CIV USARMY MEDCOM USAMRMC (USA)" <kimberly.l.odam.civ@mail.mil>, "Mendoza, Jessica L CIV USARMY MEDCOM USAMRMC (USA)" <jessica.l.mendoza19.civ@mail.mil>, "Jarrett, Raquel T CTR USARMY MEDCOM USAMRMC (USA)" <raquel.t.jarrett.ctr@mail.mil>, "Anoumatacky-Akesse Pokou, Namkpri I CTR USARMY MEDCOM USAMRMC (USA)" <namkpri.i.anoumatacky-akessepokou.ctr@mail.mil>
Subject: A-20465.e - HRPO Approval Memorandum (IRB Study Number 19-0049, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665) (UNCLASSIFIED)

CLASSIFICATION: UNCLASSIFIED

SUBJECT: Initial Approval for the Protocol, “Prevention of Post-Traumatic Contractures With Ketotifen 2 (PERK 2),” Submitted by Michael Y. Benoit, MD, University of Vermont Medical Center, Burlington, Vermont, 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, IRB Study Number 19-049, Proposal Log Number OR160026, Award Number W81XWH-17-1-0665, HRPO Log Number A-20465.e

1. The subject protocol version 3.0, dated 6 July 2018 was initially approved by the University of Vermont Institutional Review Board (IRB) on 11 December 2018. On 21 June 2019 the University of Vermont subsequently authorized the implementation of this approval. 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 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 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 20 November 2019. 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-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 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 Ismael Anoumatacky-Akesse Pokou, DDS, Human Subjects Protection Scientist, at 301-619-3190, DSN 343-3190, or namkpri.i.anoumatacky-akessepokou.ctr@mail.mil.

9. The HRPO point of contact for post-approval oversight is Raquel T. Jarrett, MPH, Human Subjects Protection Scientist, at 301-619-2380, DSN 343-2380, or raquel.t.jarrett.ctr@mail.mil.

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

Dear Dr. Kevin Hildebrand,

Please accept this letter as formal notification that I am resigning from my position as Clinical Research Coordinator with Orthopaedic Trauma Research, Surgery, Cumming School of Medicine. My last day will be Friday June 14th, 2019.

On a personal note Kevin, the support and mentoring that you provided me, made a meaningful impact on my career and personally, that I will carry with me for many years. I want to thank you for that.

Thank you very much for the opportunity to work in this position for almost 5 years. I've greatly enjoyed and appreciated the opportunities I've had, including initiating a research program at Peter Lougheed Centre, FDA IND application, Health Canada Clinical Trial application, collaborating on a US DoD grant application and of course working with the team at PLC. I've learned how to initiate/implement/maintain research trials at a site, ethics and regulatory processes, CSM legal capacities, finances and budgeting. All of which I will take with me throughout my career.

During my last 5 weeks, I'll do everything possible to wrap up my duties and train other team members. Please let me know if there's anything else I can do to aid during the transition.

I wish you and the PLC site continued success, and I plan to stay in touch in the future.

Sincerely,

Alexandra Garven

Subject: Welcome
Date: Friday, June 21, 2019 at 5:30:15 AM Mountain Daylight Time
From: Kevin A. Hildebrand
To: Gerardo Duque
CC: Jennifer Wong, Charlene Wrona

Dear Gerardo,

We are excited and very fortunate to have you joining our team as a research coordinator!

To ensure everything is ready on your first day of work, please visit the Support Staff Onboarding Checklist to begin your onboarding activities. The onboarding checklist contains information to assist you both before you start and after you arrive.

Please make note of your UCalgary UCID: 10187055.

An important first step of your UCalgary onboarding is to go to the Just Joined page and register your IT account. This will provide basic access to the university's HR system, referred to as the my.ucalgary.ca portal.
If this is not completed before your start date, it could result in delays to some of your access.
Please complete this step as soon as possible.

Finally, on your first day, please meet me at Peter Lougheed Centre, Second Cup on July 10, 2019 at 8:00 AM. The Second Cup is located by the West entrance of the complex. We will have a chat for about 30 minutes, I'll show you where your office is located and meet the other regular and summer staff working for us. You will see the physical layout and work will begin on completing your necessary U of C training, research certificates (Tricouncil policy statement 2 (TCPS-2), GCP and DIv 5 Health Canada), and Alberta Health Services training. Please feel free to contact me with any questions you have.

Best regards,

Kevin Hildebrand

Dr. Prism Schneider
Foothills Medical Centre
1403 29 St NW
Calgary, AB T2N 2T9

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

Dear Dr. Schneider:

This letter is in follow-up to my recent Site Initiation Visit performed on September 23, 2019. The initiation visit included review of the following:

- Study Personnel and Facilities
- Study Protocol/Trial Manual
- Pharmacy
- Participant Recruitment Procedures
- Informed Consent Procedures
- Urine and/or 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**
What would define a "severe" renal or hepatic impairment?	If the potential patient has to modify their medications based on disease. The patient may be on dialysis in the case of a "severe" renal impairment.
How many days pre-operatively can participant start trial medication?	As long as the participant is operative in the upcoming weeks, this does not matter. Participant must also be mobile within 21 days of injury.
What happens if participant reports an AE on the phone and inquires if they should STOP trial medication? (i.e. headache or rash)	Participant should be informed that trial medication should CONTINUE and an additional interim visit can be set up to check up on symptoms. A follow up phone call within 24 hours of initial phone call should be made to follow up on AE.

Does post-operative radiographs have to be within 24 hours of surgery?	No, these radiographs can be captured after 24 hours of operation.

We are pleased to announce that your site is now **approved to enroll** as of the September 23rd, 2019 with the pending AHS Operational Approval.

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 monitor session 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 the coordinating center following completion.	Leah Schultz
Operational Approval	Site may initiate PERK 2 recruitment without accessing patients' medical charts in any form until approval is received.	Leah Schultz

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 at 403-819-4985 or by email at hildebrk@ucalgary.ca 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

16 September 2019

Dr. Robert Chan, Qualified Investigator
Sturgeon Community Hospital
201 Boudreau Rd
St. Albert, AB T8N 6C4

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

Dear Dr. Chan:

This letter is in follow-up to my recent Site Initiation Visit performed on September 10, 2019. The initiation visit included review of the following:

- Study Personnel and Facilities
- Study Protocol/Trial Manual
- Pharmacy
- 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
- (Serious) Adverse Event and Protocol Violation Reporting

The following are responses to questions raised during the visit:

Question	**Response**
Is it possible to use $25 VISA gift cards instead of meal vouches & parking passes?	Yes, this can be done for each participant
Who can dispense medication at Pharmacy?	Pharmacists and pharmacy technicians
How will pharmacy capture temperature?	This will be logged monthly using the temp device provided by Coordinating Centre

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 monitor session after 3-5 participants are successfully randomized into the PERK 2 Trial.

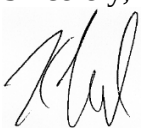
Action items to address:

Finding	**Action Required**	**Assigned To**
Trial medication in pharmacy	A photo of the trial medication is to be sent to the coordinating centre once unloaded into in-patient pharmacy shelves	Kim Fitzgerald
Training certifications required (GCP, TCPS2, Health Canada div 5, and a current signed CV)	Required training certificates for Haley Zielinski and Sub-Investigators	All staff requiring certifications
Radiographs	Inquire about having oblique (internal and external) views to be captured at each visit	Dr. Robert Chan / Anelise Silveira
Training and Delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating centre following completion	Anelise Silveira

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 at 403-819-4985 or by email at hildebrk@ucalgary.ca 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

July 04, 2019

Neil White, MD
South Health Campus
4448 Front St SE, Calgary, AB T3M 1M4
Calgary, AB T3M 1M4

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

Dear Dr. White,

This letter is in follow-up to my recent Site Initiation Visit performed on June 26, 2019. The initiation visit included review of the following:

- Study Personnel and Facilities
- Study Protocol
- Subject Recruitment Procedures
- Informed Consent Procedures
- Urine Pregnancy Testing Procedures & Logistics
- 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:**
What contact information should be on the ICF?	We would advise the removal of contact information from page 4 of 7 on current ICF which states "**In case of an adverse event where emergency unblinding needs to occur, contact 403-944-1994."**
What contact information should be used on the emergency wallet cards "In the event of an emergency or outside of normal working hours please contact:"	Currently, we are in the process of submitting a new version of the emergency wallet cards as this information is unnecessary. Participants can only request unblinding to the Sponsor, to be under review. For the time being, please add contact information for Sarah, Tina and/or Dr. White
When do follow-ups occur: following date of surgery, operation, or randomization?	Follow up visits are 2, 6, 12, 24, and 52 weeks following date of randomization

We are pleased to announce that your site (SHC Site # 05) is now **approved to enroll** as of June 26th, 2019. All screens for injuries may occur 7 days prior to this date.

We will be in touch regarding any future drug requirements, SAE reporting, and any additional PERK 2 questions your site may have.

Action items to address:

Findings	Action Required	Assigned To
Pharmacy walk-through did not occur at this visit as the research pharmacist was away from office.	Coordinate pharmacy visit with Laura Masri in July	Sarah Reitzel & Tina Samuel

We would like to schedule the first monitor session by Jackie Busheikin, our qualified PERK 2 Trial Monitor, after 3 participants are successfully randomized.

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 at 403-819-4985 or by email at hildebrk@ucalgary.ca 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. Aaron Nauth
St. Michael's Hospital
30 Bond St
Toronto, ON M5B 1W8

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

Dear Dr. Nauth:

This letter is in follow-up to my recent Site Initiation Visit performed on September 27, 2019. The initiation visit included review of the following:

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

The following are responses to questions raised during the visit:

Question	**Response**
What time points do we collect Adverse Events?	Between enrolment and 7 weeks (6 weeks of trial medication + 1 week washout). Please collect all AE's during this time period and enter on source documents & REDCap. Only report AEs that are related to trial medication to sponsor within 48 hours.
Are Adverse Events related to the injured elbow only?	Yes
What time points do we collect Serious Adverse Events?	For the entire trial period (enrolment to 52 weeks). Collect all SAEs and report all to Sponsor within 48 hours (regardless of causality to the trial medication).

We are pleased to announce that your site is now **approved to enroll** as of the date your site received 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**
Training and Delegation logs	A copy of the signed training and delegation logs to be sent to the coordinating center following completion	Lynn Vicente
Drug Tracking System	Training required – booked session on October 3rd	Taylor Stranaghan & Laura Parsons
Pharmacy – Trial Medication Storage	Following trial medication arrival, assess all 18 bottles arrived and are stored on-site	Lynn Vicente
Pharmacy – Trial Medication Temperature Log	Please ensure trial medication is temperature controlled and this is logged monthly	Site pharmacist/pharmacy technician

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 at 403-819-4985 or by email at hildebrk@ucalgary.ca 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. Pensy
University of Maryland Medical Centre
22 S Greene St
Baltimore, MD 21201, USA

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

Dear Dr. Pensy:

This letter is in follow-up to my recent Site Initiation Visit performed on September 27, 2019. The initiation visit included review of the following:

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

The following are responses to questions raised during the visit:

Question	**Response**
What time points do we collect Adverse Events?	Between enrolment and 7 weeks (6 weeks of trial medication + 1 week washout). Please collect all AE's during this time period and enter on source documents & REDCap. Only report AEs that are related to trial medication to sponsor within 48 hours.
Are Adverse Events related to the injured elbow only?	Yes
What time points do we collect Serious Adverse Events?	For the entire trial period (enrolment to 52 weeks). Collect all SAEs and report all to Sponsor within 48 hours (regardless of causality to the trial medication).

We are pleased to announce that your site is now **approved to enroll** as of the date your site receives 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 monitor session 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 the coordinating center following completion	Josh Rudnicki
Drug Tracking System training required	To be coordinated between Taylor and site pharmacists/pharmacist technician	Taylor Stranaghan and Hanna Salehi
Pharmacy – Trial Medication Storage	Following trial medication arrival, assess all 18 bottles arrived and are stored on-site	Josh Rudnicki
Pharmacy – Trial Medication Temperature Log	Please ensure trial medication is temperature controlled and this is logged monthly	Site pharmacist/pharmacy technician

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 at 403-819-4985 or by email at hildebrk@ucalgary.ca 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

SERVICES AGREEMENT

THIS AGREEMENT made as of 1 day of April 12th, 2019

BETWEEN:

JANA Research Consulting Inc.
A corporation duly incorporated under the laws of the Province of Alberta

(the "Contractor")

- and -

THE GOVERNORS OF THE UNIVERSITY OF CALGARY
a corporation created pursuant to the
Post-Secondary Learning Act, S.A. 2003, c.P-19.5,
(the "UCalgary")

WHEREAS the Contractor has skills and qualifications that the UCalgary wishes to obtain;

AND WHEREAS the UCalgary, on behalf of its faculty member Dr. Kevin Hildebrand (the "Principal Investigator"), desires to engage the Contractor to provide services to UCalgary;

AND WHEREAS the parties now wish to enter into this Agreement to set forth the terms and conditions governing the provision of services by the Contractor to the UCalgary;

NOW THEREFORE in consideration of the covenants and agreements herein contained the parties hereto agree as follows:

1. Relationship Of The Parties

(a) This is a contract for the performance of services and the Contractor is engaged under this Agreement as an independent contractor for the sole purpose of providing those services. The Contractor is not engaged by the UCalgary as an employee, servant or agent of the UCalgary. The Contractor agrees to be solely responsible for any and all applications, reports, payments, deductions or contributions required to be made including but not limited to those required for GST, or under the *Income Tax Act* (Canada), the *Employment Insurance Act (formerly Unemployment Insurance Act)* (Canada), the *Canada Pension Plan Act* (Canada) or any other statute of Canada or a province or territory thereof, in connection with the performance of the services. Contractor hereby covenants and

agrees that such remittances will be made in strict accordance with his/her statutory obligations.

(b) The Contractor indemnifies and saves harmless the UCalgary against any and all liability, loss, damages, costs or expense which the UCalgary may hereafter sustain, incur, suffer or be required to pay by reason of any assessment, re-assessment or any other act of an official of the federal or provincial governments relating to the Contractor.

2. Type Of Services

(a) Subject to the terms and conditions herein contained, the Contractor shall be obligated to provide services as listed in the attached Schedule "A" to the UCalgary and shall perform such duties and exercise such powers related thereto.

(b) The Contractor shall determine the method by which the services are performed, subject to such reasonable instructions as the UCalgary may provide from time to time.

(c) Nothing contained in this Agreement shall be interpreted or construed to prohibit or limit the right of the Contractor to provide similar services to other companies or individuals.

3. Commencement And Term

The provision of services by the Contractor will commence on April 22nd, 2019 and expire August 30th, 2023 unless terminated in accordance with the terms of Article 10 herein.

4. Performance of Services

The Contractor shall duly and diligently perform all the services to be provided by the Contractor to the UCalgary hereunder, in an efficient, workmanlike manner appropriate to the Contractor's designation, status and qualifications.

5. Remuneration

Remuneration of the Contractor shall be as set out in the attached Schedule "B".

6. Confidentiality and the Freedom of Information and Protection of Privacy Act

(a) The Contractor and the UCalgary acknowledge that this Agreement and the relationship between the Contractor and the UCalgary will be subject to the provisions of *The Freedom of Information and Protection of Privacy Act* (Alberta).

(b) In the event that proceedings under *The Freedom of Information and Protection of Privacy Act* (Alberta) are commenced respecting this Agreement or the relationship

between the Contractor and the UCalgary, and should the Contractor decide in its sole discretion to contest the disclosure of any document in respect of the foregoing, then the Contractor shall in its sole discretion appoint counsel, control the conduct of such proceedings and fund all costs associated with the conduct thereof. Notwithstanding the foregoing, the UCalgary may, at its sole cost and in its sole discretion, attend or make representations during any proceedings pursuant to *The Freedom of Information and Protection of Privacy Act* (Alberta), or otherwise exercise those rights provided to it thereunder.

(c) In the event that the Contractor obtains access to or custody of the UCalgary records, Contractor agrees to comply with the provisions of *The Freedom of Information and Protection of Privacy Act* (Alberta).

7. Confidential Information

(a) For the purposes of this Agreement, "Confidential Information" includes but is not limited to information relating to all copyrights, designs, drawings, plans, sketches, graphic representations, specifications, research, patents, trade-marks or applications therefor, inventions, know-how, secret processes, formulae, technology, techniques, procedures, test results or technical and any other information regarding the business or affairs of a party or the UCalgary's students not generally known to the public in any form whatsoever and which originated, is possessed by or controlled by the party.

(b) Each party agrees (the receiving party) that the Confidential Information of the other party (the disclosing party) is and shall be the sole and exclusive property of the disclosing party. Any Confidential Information provided by the disclosing party to the receiving party for use in the performance of this Agreement remains the property of the disclosing party and shall be returned without cost to the disclosing party upon request.

(c) The receiving party agrees to receive and hold all Confidential Information of the disclosing party in trust and confidence for the disclosing party and treat the same as confidential. The receiving party further agrees not to disclose nor give to others, both during the duration of this Agreement or thereafter, any Confidential Information of the disclosing party unless the receiving party has received the prior written authorization of the disclosing party.

(d) The obligation not to disclose Confidential Information shall not apply to Confidential Information which at the time of disclosure is readily available to the public other than through a breach of any obligation of confidentiality by the receiving party or by any other third party.

(e) The Contractor agrees to use the Confidential Information of the UCalgary only for such purposes as are required in the provision of their services to the UCalgary and agrees not to use the Confidential Information for any purpose whatsoever after the

termination of this Agreement, for any reason. The UCalgary agrees to use the Confidential Information of the Contractor only for those purposes for which the Confidential Information is provided to the UCalgary and agrees not to use the Confidential Information for any purpose whatsoever after the termination of this Agreement, for any reason.

(f) The receiving party agrees not to copy or reproduce Confidential Information of the disclosing party by any means whatsoever without the express written consent of the disclosing party or except, in the case of the Contractor, as required for the provision of Contractor's services to UCalgary.

8. Conflict of Interest Disclosure

The Contractor and all bid submissions must include full disclosures of all business relationships and includes, but not limited to, ownership interests or affiliation direct or indirect, pertaining to the project. Should a conflict of interest exist or arise, as determined solely by the UCalgary, the UCalgary, at its sole discretion, may immediately terminate this Agreement.

9. Ownership

(a) Any information, data, documents and materials provided by the UCalgary to the Contractor for use in the performance of this Agreement shall remain the property of the UCalgary and shall be returned without cost to the UCalgary upon request.

(b) Any information, data, research, documents, photographs, negatives, computer programs (and related object and source codes), and any other materials produced by the Contractor or any officers, employees, or agents of the Contractor, in the performance of this Agreement and all patents and copyright therein, shall be the exclusive property of the Contractor. Title to and ownership of all intellectual property in any software provided by Contractor or created by the Contractor shall at all times remain with Contractor and the UCalgary shall not have any right, title or ownership interest therein except the right to use that software as provided herein.

(c) Contractor shall provide to the UCalgary a copy of all data, research, documents, photographs, negatives, and any other materials produced by the Contractor or any officers, employees, or agents of the Contractor, in the performance of this Agreement, provided Contractor shall have no obligation to provide any material relating to any of its software, including source code, algorithms and architecture.

(d) If the Services identified in Appendix "A" include access to computer programs, the Contractor will deliver to the UCalgary a copy of the related object code (no source code will be provided) for use by the UCalgary as follows. Contractor hereby grants, and UCalgary hereby accepts, subject to the terms and on the conditions set forth in this Agreement, a non-exclusive and non-assignable license

for the one or more researchers and/or investigators that Contractors is working directly with to use the Software during the term of the services as set out in Section 3. At the end of such term, such researchers and/or investigators shall cease all use of software and the UCalgary shall delete or return all copies of the software to Contractor. At the request of the UCalgary, the parties shall negotiate in good faith the UCalgary purchasing a license to the Software, which will generally be based on the terms and conditions Contractor charges similar clients for the Software.

10. Provisions Which Operate Following Termination

Notwithstanding any termination of this Agreement for any reason whatsoever, the provisions of Section 7, of this Agreement and any other provisions of this Agreement necessary to give efficacy thereto shall continue in full force and effect following such termination.

11. Termination

(a) Either party may terminate this Agreement at any time upon the provision of **one month** notice to the other party prior to the termination date; and

(b) If the Contractor should commit an act of bankruptcy or be adjudged bankrupt or make a general assignment for the benefit of creditors, or if a receiver is appointed over all or a material portion of the business and assets of the Contractor, or if the Contractor has abandoned performance of the services or has made an assignment of this Contract without the prior written consent of the UCalgary, the UCalgary may terminate this Agreement, without prejudice to any other right or remedy the UCalgary may have, by giving notice of such termination to the Contractor or to the Contractor's receiver or trustee in bankruptcy.

(c) If the Contractor fails in any respect to perform the services or any portion thereof with promptness and diligence and otherwise in accordance with the terms of this Agreement and such failure continues for ten (10) days following notice of default, then the UCalgary may, without prejudice to any other right or remedy the UCalgary may have, notify the Contractor that the Contractor is in default hereunder, providing a reasonable description of the nature of such default, and instruct the Contractor to correct such default.

(d) Upon the occurrence of a default under Section 11(c), the UCalgary may, without prejudice to any other rights or remedies the UCalgary may have terminate the Contractor's right to continue performance of the Contract in whole or in part.

12. Obligations of the Contractor

The obligations of the Contractor are as listed in the attached Schedule "A".

13. Intentionally removed

14. Insurance

"The Contractor may, at its sole discretion, but is not obliged to, procure or maintain insurance coverage for the Contractor and the Contractor's belongings. In such event, the Contractor shall be solely responsible for procuring, maintaining and paying for such insurance coverage.

The Contractor may, as required by applicable law, procure and maintain its own Workers' Compensation Insurance. In such event, the Contractor shall be solely responsible for procuring, maintaining and paying for such Workers' Compensation Insurance

15. Limited Warranty and Limitation of Liability

The Contractor shall indemnify and hold harmless the UCalgary, its directors, officers, employees and representatives from any and all damages, judgements, claims, fines, actions, incurred by the UCalgary which are based upon or arise out of any wrongful or negligent acts of the Contractor.

Contractor warrants to UCalgary for a period of ninety (90) days from the date of performance of any service, that the service will have been performed in a good and workman-like manner. If the services were not performed as warranted and UCalgary provides notice of such deficiency within that warranty period then Contractor shall reperform the services so that they are in compliance with such standard. The foregoing shall be UCalgary's only remedy or recourse against Contractor and Contractor's only obligation and liability in relation to any failure of or defect in any service whatsoever.

THE WARRANTIES STATED ABOVE ARE THE SOLE AND EXCLUSIVE WARRANTIES AND REMEDIES OFFERED BY CONTRACTOR IN CONNECTION WITH THE SERVICES AND SOFTWARE. THERE ARE NO OTHER WARRANTIES OR CONDITIONS, EXPRESS, IMPLIED OR STATUTORY INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OR CONDITION OF CORRECTNESS OR PERFORMANCE OR MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE AND CONTRACTOR SPECIFICALLY DISCLAIMS ANY WARRANTIES OR CONDITIONS THAT MAY BE IMPLIED BY STATUTE.

UNDER NO CIRCUMSTANCE SHALL CONTRACTOR BE LIABLE FOR ANY INCIDENTAL, SPECIAL, INDIRECT OR CONSEQUENTIAL DAMAGES OR LOSSES WHICH MAY BE SUFFERED OR INCURRED BY THE UCALGARY ARISING IN CONNECTION WITH THIS AGREEMENT, INCLUDING ARISE OUT OF ANY FAILURE, ERROR OR DEFECT IN THE SERVICES OR SOFTWARE, WHETHER OR NOT CONTRACTOR WAS TOLD OF THE POSSIBILITY OF SAME.

IN ALL CIRCUMSTANCES, CONTRACTOR'S TOTAL MAXIMUM AGGREGATE LIABILITY UNDER THIS AGREEMENT, ARISING IN ANY MANNER

WHATSOEVER, SHALL BE LIMITED TO THE TOTAL OF THE MONIES PAID BY UCALGARY TO CONTRACTOR UNDER THIS AGREEMENT.

16. Assignment

The Contractor shall not assign or delegate any of its rights or obligations under this Agreement without the UCalgary's prior written consent. Any assignment or delegation in violation of this provision is void.

17. Sections and Headings

The division of this Agreement into Articles and Sections and the insertion of headings are for the convenience of reference only and shall not affect the construction or interpretation of this Agreement. The terms "this Agreement", "hereof", "hereunder", "thereunder" and similar expressions refer to this Agreement and not to any particular Article, Section or other portion hereof and include any agreement or instrument supplemental or ancillary hereto.

18. Entire Agreement

This Agreement constitutes the entire agreement between the parties with respect to the subject matter hereof and cancels and supersedes any prior understandings and agreements between the parties hereto with respect thereto. There are no representations, warranties, forms, conditions, undertakings or collateral agreements, express, implied or statutory between the parties other than as expressly set forth in this Agreement.

19. Amendments and Waivers

No amendment to this Agreement shall be valid or binding unless set forth in writing and duly executed by both of the parties hereto.

20. Notices

Notices shall be deemed to be effective if sent by facsimile on the day it was sent or if sent by registered mail, five days after having been sent. Notices shall be sent to:

To the Contractor:

Jacqueline Busheikin
JANA Research Consulting Inc.
636 Woodpark Cr. SW
Calgary, Alberta, Canada T2W 2S2

To the UCalgary:

The Governors of the University of Calgary

Legal, Research Services – CSM
Rm G363B, Ground Floor, HSC Building
3280 Hospital Drive NW
Calgary, Alberta, Canada T2N 4Z6
Attn: Manager
Tel: 403-210-7813
Fax: 403-210-6677
Email: csmlegal@ucalgary.ca

To Principal Investigator:

Dr. Kevin Hildebrand
Health Research Innovation Centre
3280 Hospital Drive NW
Calgary, Alberta T2N 4Z 6
Ph: 403-220-7282: Fax: 403-270-3679
email: hildebrk@ucalgary.ca

21. Severability

If any provision of this Agreement is determined to be invalid or unenforceable in whole or in part, such invalidity or unenforceability shall attach only to such provision or part thereof and the remaining part of such provision and all other provisions hereof shall continue in full force and effect.

22. Number

In this Agreement words importing the singular number only shall include the plural and *vice versa* and words importing the masculine gender shall include the feminine and neuter genders and *vice versa* and words importing persons shall include individuals, partnerships, associations, trusts, unincorporated organizations and corporations and *vice versa.*

23. Schedules

Schedule A and B are the Schedules annexed hereto and incorporated by reference and deemed to be part of this agreement.

24. Governing Law

This Agreement shall be governed by and construed in accordance with the laws of the Province of Alberta and the laws of Canada applicable therein.

Signature page to follow.

CONTRACTOR

Signature

30 JUN 2019

Jacqueline Busheikin
President, JANA Research Consulting Inc.

THE GOVERNORS OF THE UNIVERSITY OF CALGARY

Signature

JUN 13 2019

Dr. Robert Ian Thompson
Associate Vice President (Research)

SCHEDULE "A"

Contractor agrees to provide to UCalgary/ Principal Investigator clinical research monitoring services as follows:

a) Initial consultation and protocol review to discuss the plan;
b) Ongoing review, via site visits, at intervals agreed to between the parties and defined in the Monitoring Plan, including review of applicable informed consent forms and processes, source document review of pre-determined key data points, remote review of case report forms and review of compliance with protocol for key predetermined procedures.
c) Written report to UCalgary/ Principal Investigator within ten (10) business days of each site visit, with significant Good Clinical Practice or protocol deviations to be communicated to the UCalgary/Principal Investigator, via telephone or e-mail, within 2 business days of the site visit.
d) Contractor will make site visits to participating research sites as per Monitoring Plan. Actual time at site may vary from site to site and with type of visit. Duration of Site visits will include door-to-door travel time

SCHEDULE "B"

UCalgary/Principal Investigator shall compensate Contractor for the performance of the services described in Schedule A, at the rate of One Hundred Dollars ($100.00) CAD per hour. The said rate shall apply to time spent in conducting on-site visits, compiling reports, additional consultations with UCalgary/Principal Investigator and travel time. In addition, UCalgary/Principal Investigator agrees to reimburse Contractor promptly for reasonable expenses incurred by Contractor in the performance of the services, such as, but not limited to travel costs and parking. Unless otherwise specified in writing by Contractor, payment of all billings for such services and reasonable expenses shall be made within thirty (30) days of the submission of billings by Contractor.

Invoices should be sent to:
University of Calgary
RE: PERK 2 Trial Dr. Kevin Hildebrand
2500 University Drive NW
Calgary, AB T2N 1N4
Canada
Att: Alexandra Garven
Email: Alexandra.Garven@albertahealthservices.ca

Risk Based Monitoring Plan: Investigator-Initiated Clinical Trials

Version 1.0 Oct 08, 2019

Trial Title:	PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2)	**NCT#:**	03582176
		IND#:	136411
		Protocol Code:	PERK2_KAH
Investigational Product (IP):	Ketotifen fumarate (2 mg or 5 mg) or lactose placebo (bottle contains 84 capsules)		
Sponsor:	University of Calgary/Dr. Kevin A. Hildebrand		
Coordinating Centre:	Peter Lougheed Centre 3500 26 Avenue NW Calgary, AB T1Y 6J4 Research Coordinator: Gerardo Duque Ph: 403 – 943 – 5556 E: gerardo.duque@ucalgary.ca Research Assistant: Taylor Stranaghan Ph: 403 – 943 – 5536 E: taylor.stranaghan@ucalgary.ca		
Principal Investigator:	Dr. Kevin A. Hildebrand		

The following document has been referenced to FDA Guidance on Risk-Based Approach to Monitoring

Table of Contents

List of Abbreviations…… 3

1.0 Introduction…….. 4

2.0 Purpose……. 4

3.0 Monitoring Methods……. 4

3.1 On-Site Monitoring……..……. 4

3.2 Centralized Monitoring……. 4

4.0 Monitoring Visits…….. 4

4.1 Interim Visits…… 4

4.11 On-Site Interim Visit…… 5

4.12 Centralized Interim Visits…… 7

4.2 Close-Out Visit……..…….. 7

5.0 Non-Compliance…….. 8

6.0 Monitor Report……. 8

List of Abbreviations

AE	Adverse Event
DoD	Department of Defense
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HC	Health Canada
HRPO	Human Research Protection Official
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IRB	Institutional Research Board
PI	Primary Investigator
QI	Qualified Investigator
REB	Research Ethics Board
ROM	Range of Motion
SAE	Serious Adverse Event
SDV	Source Document Verification
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

1.0 Introduction

This document identifies key monitoring activities and specifies the data to be reviewed. Trial monitoring is a Sponsor responsibility as outlined in the International Conference on Harmonization Good Clinical Practice (ICH-GCP) and has been delegated by Dr. Kevin Hildebrand/University of Calgary to an independent monitor and/or a delegated member of the PERK 2 research team.

2.0 Purpose

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human participants are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol, Good Clinical Practice (GCP), and applicable regulatory requirements

3.0 Monitoring Methods

3.1 On-Site Monitoring

On-site monitoring is an in-person evaluation carried out by the trial monitor at the local site where clinical investigation is being conducted. On-site monitoring verifies that all randomized participants are legitimate, and that all source documentation transcribed into the electronic data capturing (EDC) system (REDcap) is accurate.

3.2 Centralized Monitoring

Centralized monitoring is a remote evaluation carried out by the trial monitor without having to visit the local site. The monitor will verify electronic documentation through access of online database (REDCap). Centralized review will occur every 6 months depending on the recruitment rate at the site and quality of overall conduct of the trial. Centralized monitoring verifies that EDC system entry completion processes are followed and up to date, data quality control process are followed (data edit checks, missing data, batch queries), and timely follow-up in query creation & resolution is maintained.

4.0 Monitoring Visits

4.1 Interim Visits

Frequency of interim monitoring visits will be based on enrollment status, safety concerns, data quality, and protocol compliance. Two types of interim visits will take place throughout the course of the trial.

4.11 On-Site Interim Visit

There will be one on-site interim visit which is conducted by the independent monitor. This visit is scheduled after initial 3-5 participants have been randomized (or after first participant reaches 12 weeks). Additional on-site interim visits will occur in situations of identified data anomalies, high frequency of errors, protocol violations, high participant withdrawal rates, or as identified by the Sponsor. The purpose of this visit is to ensure source documentation, as outlined below, can be verified in-person.

Focus of On-Site Interim Monitoring Visit:

The following documents are source document verified (SDV) by the trial monitor for all participants enrolled at the time of visit or for the initial 5 participants enrolled if there are more than 5 participants enrolled at the time of visit:

1. Screening Forms
    - Enrolled participants meet all inclusion and exclusion criteria
    - all inclusion and exclusion criteria is verified with source documentation
2. Consent Forms
    - Original signed consent (not copy version) present on site; all pages present
    - The current REB/IRB approved version of consent document was signed and dated by participant, research staff delegate, and (if necessary) a witness
    - Consent was obtained prior to initiation of any trial procedures
    - All appropriate signatures and dates were obtained prior to initiation any trial procedures
    - Re-consenting with updated consent forms (if applicable and as directed by REB/IRB) completed in a timely manner (i.e. at their next visit at the latest)
    - Copy of signed consent form provided to participant
3. Urine pregnancy testing documentation
    - Verify all urine (or blood) pregnancy tests are performed on female participants of child-bearing age
        i. Source documentation includes: Result of test, lot #, expiration date, signature from attending surgeon and nurse/orthopaedic technician performing test
4. Pill count (2- and 6-week)
    - Verify that pill count has been recorded at 2- and 6-week time points
    - 2-week pill count ≥70 pills flagged to enure drug compliance is maintained

5. 12 week ROM assessment
    - Verify completion of 12 week visit range of motion measurements
    - Verify accurate transcription of data into REDCap
    - Verify accurate range of motion parameters are used
6. Serious Adverse Events (re-operative reports)
    - Verify all newly reported SAEs against source documentation
    - Follow up on previously reported SAEs
    - Confirm that all SAEs have been reported according to local REB/IRB policy, as well as to the sponsor within 48 hours
    - Identify any unreported SAEs in source documentation and ensure reporting process is initiated
7. Protocol Violation Form
    - Verify all newly reported protocol violations against source documentation
    - Follow up on previously reported protocol violations
    - Confirm that all protocol violations have been reported according to local REB/IRB policy, as well as to the sponsor within 48 hours
    - Identify any unreported protocol violations in source documentation and ensure reporting process is initiated
8. Participant Withdrawal Form
    - Verify completion of form
    - Verify withdrawal type (full or partial)
        i. Full – no use of any data
        ii. Partial – stop drug, continue follow up and collect data
        iii. Partial – stop drug and follow up visits, allow continued data collection via chart reviews
        iv. Partial – stop drug, follow up visits, and future data collection. Allow previously collected data to be used
9. Pharmacy
    - Confirm that investigational product is stored at the correct temperature in a secure storage area.
    - Verify any temperature excursions (outside of 15-25◦C) have been reported to the Sponsor within 24 hours of identifying excursion
    - Signed medication request forms are complete and stored in pharmacy
    - Confirm that trial medication is being dispensed according to current protocol
    - Confirm that product inventory and destruction records are accurate, current, and reconciled
    - Ensure no discrepancies exist between drug logs and Drug Tracking System
    - Ensure drug log documentation is completed in chronological order in a timely fashions

- Ensure the balance on the drug inventory log matches the inventory balance
- Ensure all shipment receipts are retained
- Ensure product is returned/destroyed as mandated by protocol
- Ensure no products is returned/destroyed prior to authorization to proceed
- Ensure product return/destruction documents are retained on logs

4.12 Centralized Interim Visits

Centralized interim visits are conducted by a delegated research team member and will be completed every 6 months following the initial on-site monitoring visit. Higher frequency visits will occur in situations of identified data anomalies, high frequency of errors, protocol violations, high participant withdrawal rates, or as identified by the Sponsor.

Focus of Centralized Interim Monitoring Visit:

The purpose is to ensure accuracy and completeness of the transcription of source documentation into the EDC system (REDCap) of all currenently enrolled participants. Query generation will be accomplished at this time to address any discrepencies in the data.

Data Review:

1. Case Report Forms
    a. Baseline form
    b. Operative report
    c. Follow up visit forms
    d. Patient Reported Outcome Measures (DASH, OES, and PCS)

Unreviewed Data:

1. Phone call visits
2. Adverse events
3. Concomitant medication
4. Interim visit(s)

4.2 Close-out Visit

A centralized final close out visit will be conducted by a delegated research team member once the final randomized participant reaches their 52-week visit.

Focus of close-out monitoring visit:

- Ensure the completion of all outstanding source documents
- All queries have been adequately resolved in the REDCap database
- Ensure all previous monitoring corrections have been addressed

- Ensure the return or destruction of any outstanding trial medication v
- Collection of the completed delegation and training logs (via corrier)
- Review the plans and location for record retention
- Ensure all SAEs have been recorded and reported appropriately
- Ensure the QI has notified the local REB of the site closure

5.0 Non-Compliance

Non-compliant conduct of the trial will be documented in a monitoring report and forwarded to the Sponsor. It is the responsibility of each QI to address all observations outlined in the monitoring report and ensure appropriate and compliant procedures are implemented in a timely manner.

6.0 Monitor Report

The independent montor will generate a report on the material covered in the primary on-site visit and any additional training required following the visit. The report will be sent to the Sponsor within 14 days of the visit. Any additional comments/concerns can be addressed and reported back to the monitor at this time. A finalized copy of the report is then sent to the Sponsor. A follow-up letter will be generated by the independent monitor and sent to the site QI and site Coordinator. Any additional concerns from the site will be followed up by the coordinating centre. Follow up centralized monitoring reports will be generated by a delegated member of the research team following the same describe process as above.

Gerardo Duque

From: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
Sent: Friday, September 13, 2019 9:33 AM
To: 'Jackie Busheikin'
Cc: Gerardo Duque; Kevin A. Hildebrand
Subject: RE: PERK 2 Monitoring

Hi Jackie,

10:00 am meeting at Second Cup works well for me.
Sounds great, thanks for all your help!

Talk to you soon,
Taylor

From: Jackie Busheikin [mailto:jackie.busheikin@gmail.com]
Sent: Friday, September 13, 2019 9:28 AM
To: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
Cc: Gerardo Duque <gerardo.duque@ucalgary.ca>; hildebrk@ucalgary.ca
Subject: Re: PERK 2 Monitoring

Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

HI Taylor,

That will be fine. I will be there for 10 am - let me know where to go or if you want to meet me. I will put together a draft monitoring report for your team to look at and will send that out to you next week.

Jackie

On Fri, Sep 13, 2019 at 9:24 AM Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca> wrote:

> Hi Jackie,
>
> The 16th of October would work best for me as I don't have any patients in clinic that day, would 10:00am work for you? Yes we will ensure you have access to the EDC system on this day as well.
>
> Thanks,
>
> Taylor

From: Jackie Busheikin [mailto:jackie.busheikin@gmail.com]
Sent: Friday, September 13, 2019 9:15 AM
To: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
Cc: hildebrk@ucalgary.ca; Gerardo Duque <gerardo.duque@ucalgary.ca>
Subject: Re: PERK 2 Monitoring

Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

Hi Taylor,

Thanks for the reply.

Since the 14th is Thanksgiving, the 15th would be the best date for me - I will be away after the 17th. I could come on the 16th if you can't meet with me on the 15th. the other thing I will need is access to your EDC and perhaps a contact to walk me through the system briefly with regards to the monitoring process (how to enter queries etc.) If you or Gerardo can do that, that would be great,

Jackie

On Fri, Sep 13, 2019 at 8:41 AM Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca> wrote:

> Hi Jackie,
>
> Thanks again for the visit with us and to review our monitoring plan – you're guidance is always incredibly valuable!
>
> I am in the process of updating our current Monitor plan with the changes discussed. Once this is complete I will send it to you for any further comments (along with our revised and submitted protocol).
>
> In terms of our monitoring visit at PLC, I believe mid – October would be sufficient having 2 participants reaching their 12 week visits. What day works best for you either in the week of October 14th or October 21st?

Thank you,

Taylor

From: Jackie Busheikin [mailto:jackie.busheikin@gmail.com]
Sent: Friday, September 13, 2019 7:54 AM
To: hildebrk@ucalgary.ca; Gerardo Duque <gerardo.duque@ucalgary.ca>; Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
Subject: PERK 2 Monitoring

Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

Hi Taylor and team,

Following up on our meeting last week, I wanted to summarize my understanding of the next steps in the plans as things are moving forward:

- revision to Draft monitoring plan will be made by Taylor

- Jackie will develop a monitoring tool to use for site visits based on the current draft as well as our discussion.

- the team will send Jackie a copy of the revised protocol when it is submitted to the REB.

- since there are 3 subjects currently at PLC, a monitoring visit should be booked to take place i early October . Taylor was going to check on when that subject will reach week 12 but this will provide us an opportunity to do a run-through of a visit and identify any items needing clarification as well as a sense of the time requirements on site. Let me know what that scheduling looks like as soon as possible.

Please remind me if there is anything I have missed.

Kind Regards,

Jackie Busheikin

This message and any attached documents are only for the use of the intended recipient(s), are confidential and may contain privileged information. Any unauthorized review, use, retransmission, or other disclosure is strictly prohibited. If you have received this message in error, please notify the sender immediately, and then delete the original message. Thank you.

Gerardo Duque

From: Jackie Busheikin <jbusheikin@janaresearch.com>
Sent: Tuesday, October 15, 2019 8:57 AM
To: Taylor Stranaghan
Cc: Gerardo Duque
Subject: Re: PERK 2

Thanks very much.

Jackie Busheikin

JANA Research Consulting Inc Ph: 403-861-8033 jbusheikin@janaresearch.com

On Tue, Oct 15, 2019 at 8:23 AM Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca> wrote:

> Hi Jackie,
>
> That is the South Health Campus in Calgary. The lead coordinator is Sarah Reitzel (slreitze@ucalgary.ca) and their Qualified Investigator is Dr. Neil White (neiljwhite@gmail.com).
>
> I have attached a list of coordinators and QI for each site that Gerry has made. That is correct, during the SIV I inform the sites about the initial on-site monitoring visit.
>
> See you tomorrow,
>
> Taylor
>
> **From:** Jackie Busheikin [mailto:jbusheikin@janaresearch.com]
> **Sent:** Tuesday, October 15, 2019 7:37 AM
> **To:** gerardo.duque@ucalgary.ca; Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
> **Subject:** PERK 2
>
> Caution - This email came from an external address and may contain unsafe content. Ensure you trust this sender before opening attachments or clicking any links in this message.

Hi Gerardo and Taylor.

When I was pouring for tomorrow's visit I noted from Redcap that S. Calgary also has a subject post week 12 so they should have also had a monitoring visit. At this point I cannot get there before mid November but if you could please give me the contact info - study coordinator and QI, I will contact them and book something for mid November.

Moving forward, we will need a method for you to let me know when sites have enrolled their 3rd subject so I can track that. I will also need the SC and QI names for each of the other sites at that time. I am assuming that all sites will have been notified that I am coming.

Thanks so much - Taylor I will see you tomorrow just before 10 at second cup.

This message and any attached documents are only for the use of the intended recipient(s), are confidential and may contain privileged information. Any unauthorized review, use, retransmission, or other disclosure is strictly prohibited. If you have received this message in error, please notify the sender immediately, and then delete the original message. Thank you.

CONTENT	DETAIL
Introduction	
Name of trial plus (ClinicalTrials.gov number)	PrEvention of posttraumatic contractuRes with Ketotifen 2 – PERK 2 (NCT03582176)
Study Sponsor / Principal Investigator	University of Calgary / Kevin A. Hildebrand
Funding Agency	US Department of Defense – Congressionally Directed Medical Research Programs
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 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.
Roles and responsibilities	
A broad statement of the aims of the committee	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.
Terms of reference	The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the TSC.
Specific roles of DMC	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)

CONTENT	DETAIL
	• 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) *a priori* 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)
Before, or early in to, the trial	
Whether the DMC will have input into the protocol	All potential DMC members will have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have 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.
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. The first report should contain tables and graphs based on real data wherever possible. Consideration should be given to shell (empty) tables for the data not yet available. One aim of meeting is to familiarise the DMC members with the format that will be used in the reports and to give them the opportunity to suggest changes and additions.
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.

CONTENT	DETAIL
Composition	
Membership and size of the DMC	The membership will consist 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). Note: "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
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 (***TBA***), 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.
The responsibilities of the trial statistician	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 responsibilities of the trial office team	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 responsibilities of the PI and other members of the TMG	The PI, Kevin A. Hildebrand, may be asked and should be available to attend open sessions of the DMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).

CONTENT	DETAIL
Relationships	
Relationships with Principal Investigators, other trial committees (e.g. Trial Steering Committee (TSC) or Executive Committee), sponsor and regulatory bodies	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.
Clarification of whether the DMC are advisory (make recommendations) or executive (make decisions)	The DMC is advisory to the TSC. The TSC is the executive body for the trial.
Any payments to DMC members	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.
The need for DMC members to disclose information about any competing interests	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	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.
Whether meetings will be face-to-face or by teleconference	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.
How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	**Definitions** Closed session: Only DMC members, and the trial statistician should be present in closed sessions (although the DMC should be able to ask others to leave, also). Sessions attended only by DMC members may be referred to as executive sessions. Open session: Attended by those at the closed session, plus the PI(s), and perhaps also representatives of the sponsor, funder, or regulator, as relevant. Those attending only the open session may attend via videoconference or, if appropriate by phone. The format will be:

CONTENT	DETAIL
	1 Closed session: All parts of the report are discussed, and DMC discussion (± 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) **3 Closed session: extra closed session if necessary.**
Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Open sessions: 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.
Intended content of material to be available in closed sessions	Closed sessions: 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.
Will the DMC be blinded to the treatment allocation?	The DMC will not be blinded to the identity of the treatment arms.
Who will see the accumulating data and interim analysis?	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.
Who will be responsible for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	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.
To whom the DMC will communicate the decisions/recommendations that are reached	The DMC will report its recommendations in writing to the Trial Steering Committee. This should be copied to the trial statistician (or trial manager) and should be sent via the trial office team to coincide with TSC meetings. If the trial is to continue largely unchanged then it is often useful for the report from the DMC to include a summary paragraph suitable for trial promotion purposes. (See Appendix 2).
Whether reports to the DMC be available before the meeting or only at/during the meeting	It is planned that the DMC will receive the report from the trial office team at least 2 weeks before any meetings.
What will happen to the confidential papers after the meeting	The DMC members should store the reports safely after each meeting so they may check against the next report. After the trial is reported, the DMC members should destroy all interim reports.
Decision making	
What decisions/recommendations will be open to the DMC	The possible recommendations are numerous and could include:-

CONTENT	DETAIL
	• No action needed, trial continues as planned • Early stopping due to, amongst other things, clear benefit or harm of a treatment, safety concerns on secondary outcome, futility, slow recruitment, or external evidence • Stopping recruitment within a subgroup • Extension of recruitment or follow-up • Advising on or proposing protocol changes Note: The DMC will not advise on changes to the target sample size that are based on emerging differences between the trial arms. [ψ]
The role of formal statistical methods, specifically which methods will be used and whether they will be used as guidelines or rules	A recommendation to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community. No formal interim statistical analyses of the principal outcome measure are planned. It is expected that the trial will terminate when the intended sample size has been achieved.
How decisions or recommendations will be reached within the DMC	The role of the chair should be to summarise discussions and encourage consensus. In each area of discussion the chair should give their own opinion last. Every effort should be made for the DMC to reach a consensus. If the DMC cannot achieve consensus, a vote should be taken, although details of the vote should not be routinely included in the report to the TSC, as it may inappropriately convey information about the state of the trial data.
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	The DMC should report in writing to the Trial Steering Committee, usually within 3 weeks after the meeting. This should be copied to the trial statistician and may be sent via the trial office team.

[ψ] 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
	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.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	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.
What will be done in the instances of disagreement between the DMC and the body to which they report	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.
After the trial	
Publication of results	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.
The information about the DMC that will be included in published trial reports	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.
Whether the DMC will have the opportunity to approve publications, especially with respect to reporting of any DMC recommendation regarding termination of a trial	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. Trial Steering Committee, trial investigators).

CONTENT	DETAIL
Any constraints on DMC members divulging information about their deliberations after the trial has been published	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

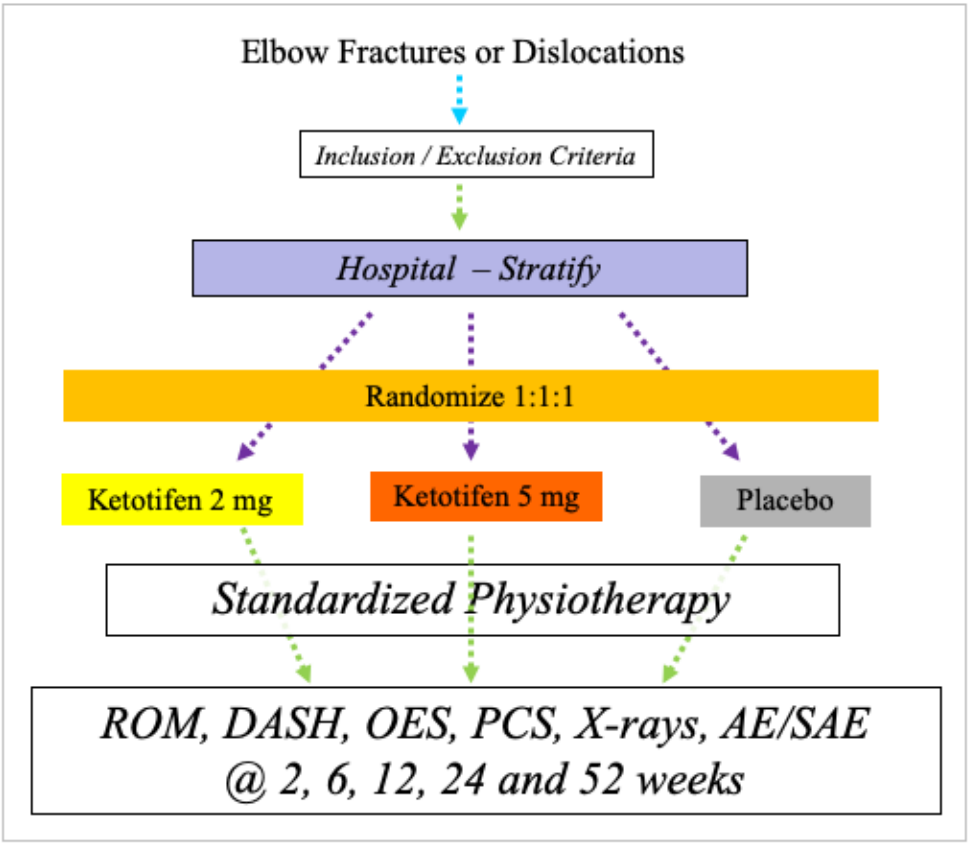
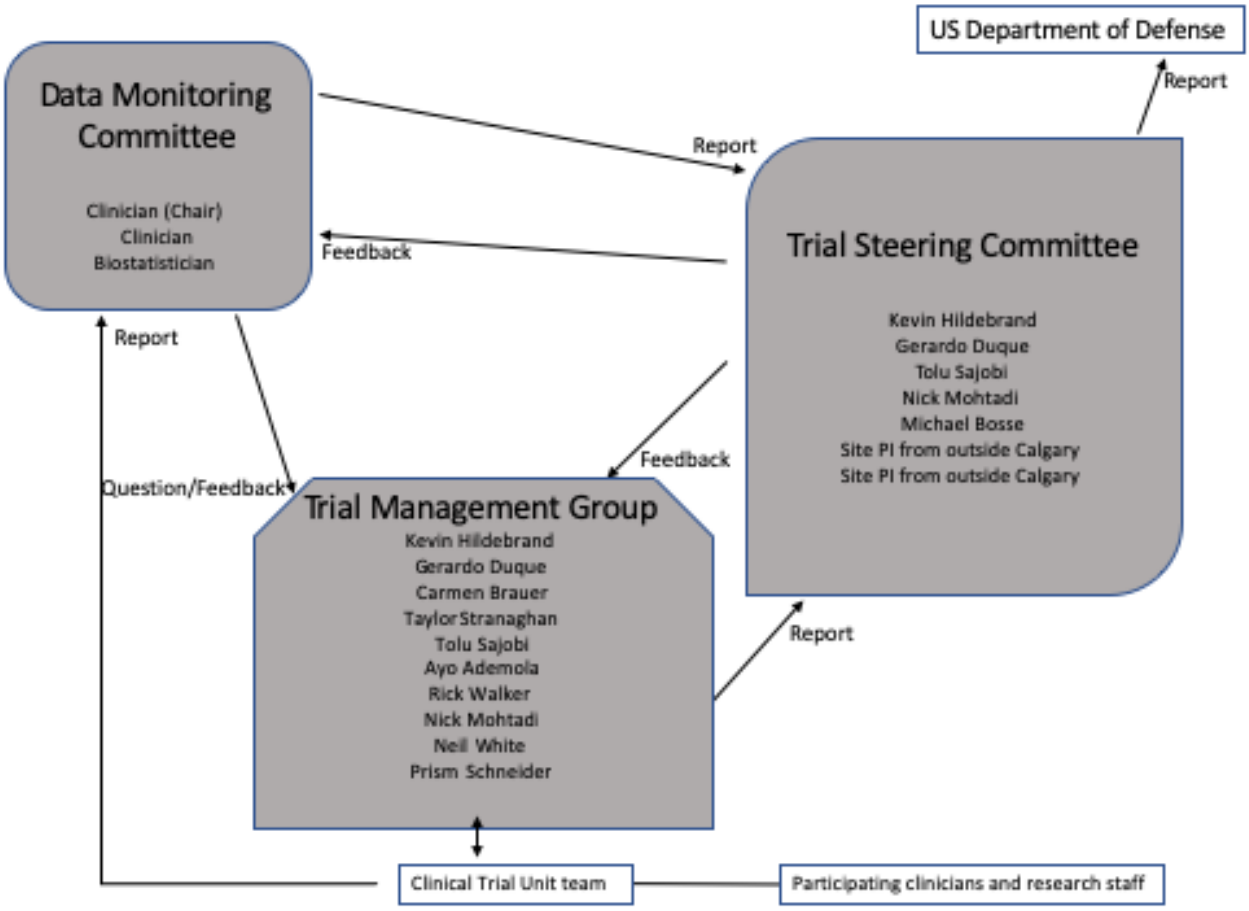


Figure 2: Relationships between trial committees



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: Suggested report from DMC to TSC where no recommendations are being made

[Insert date]

To: Kevin Hildebrand, Chair
PERK 2 Trial Steering Committee

Dear Dr Hildebrand,

The Data Monitoring Committee (DMC) for the ***PERK 2*** trial met on *[meeting date]* to review its progress and interim data. *[List members]* were able to attend the meeting and review the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

Dr *[Chairman's name]*

Chairman of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:

- (Clinician), City
- (Clinician), City
- (Statistician), City

Appendix 3: 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 1.0, June 23, 2019

(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:	23-Jun-2019

Prepared by

Name:	Kevin Hildebrand	Role:	Chief Investigator
Signature:		Date:	23-Jun-2019

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.

CONTENT	DETAILS OF TMG
Any other issues specific to the treatment under study Whether members of the TMG will have a contract	Operative management of the elbow injuries is at the discretion of the participant in conjunction with the responsible site surgeon. TMG members will not formally sign a contract. They should formally register their agreement to join the group by confirming (1) that they agree to be on the TMG and (2) that they agree with the contents of this Charter. Members should complete and return the form in Annexe 1.
4. Composition	
Membership and size of the TMG	The members of the TMG for this trial are: (1) Kevin Hildebrand – Chief Investigator (2) Gerardo Duque – Trial Manager (3) Carmen Brauer – Adverse Event Chair (4) Taylor Stranaghan – Research Assistant (5) Tolulope Sajobi – Trial Statistician (6) Ayoola Ademola – Data Manager (7) Richard Walker – Diagnostic Imaging (8) Nicholas Mohtadi – Clinical Trialist (9) Neil White - Clinician (10) Prism Schneider - Clinician Members of the TMG should disclose potential competing interests (see Section 5).
The Chair, and the Chair's role (Likewise, if relevant, the vice-Chairman)	The Chair of the TMG will be the CI of the trial – Kevin Hildebrand. The CI will be a member of the TSC and must attend all TSC meetings. The CI should be available to attend IDMC meetings. The other TMG members will not usually be expected to routinely attend TSC or IDMC meetings but may attend sessions when necessary and appropriate. The vice-Chair will assume the responsibilities of the Chair when the Chair is not available. The Vice-Chair is Neil White.
The responsibilities of the clinical trials unit (CTU) team	The CTU team (Trial Manager – Gerardo Duque and Research Assistant – Taylor Stranaghan, Ayoola Ademola – Data Manager) will be responsible for running the trial on a day-to-day basis, maintaining trial databases, randomising patients, ensuring complete and correct data, preparing short reports for meetings (including those of the TMG) and dealing with research governance and, if appropriate, regulatory matters.
5. Relationships	
Relationships with the other trial committees (e.g. Trial Steering Committee, TSC), Sponsor and regulatory bodies	The responsibilities of each trial committee are detailed in the protocol. The relationships between these groups are displayed in Figure 2.
Advisory and executive bodies	The TSC is the oversight body and is delegated this role by the Sponsor. All substantial issues regarding the trial must be referred to the TSC for consideration. The IDMC is advisory to the TSC.
The need for TMG members to disclose information about any potential competing interests	Members of the TMG should disclose potential competing interests (other than an intellectual involvement in the trial) which may be perceived by some as preventing them from making decisions to the benefit of the trial. Potential competing interests are not restricted to financial matters – involvement in other trials or involvement with pharma could be relevant, for example they have an ongoing advisory role to a company providing drugs to the trial. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annexe 1). This 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 frequency will be every 2 months. This will be shortened or lengthened as necessary related to trial needs and agreement with TMG members.

CONTENT	DETAILS OF TMG
Meeting setting When the TMG is quorate	Face-to-face meetings will normally be held, with teleconference options. Meetings will be organised by CTU staff. (See Section 8)
Can TMG members who cannot attend the meeting provide input What happens to members who do not attend meetings	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 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 people who will see accumulating trial data and interim analysis	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.
Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	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.
What will happen to the reports and papers	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) • 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:-

CONTENT	DETAILS OF TMG
	• 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
How decisions will be reached within the TMG	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.
When the TMG is quorate	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	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.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	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.
What will be done if there is disagreement between the TMG and TSC	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	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.
The information about the TMG that will be included in published trial reports	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.
Any constraints on TMG members divulging information about their trial experiences	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
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
SAE	Serious adverse event
SAR	Serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

Figure 1: Diagram summarizing trial

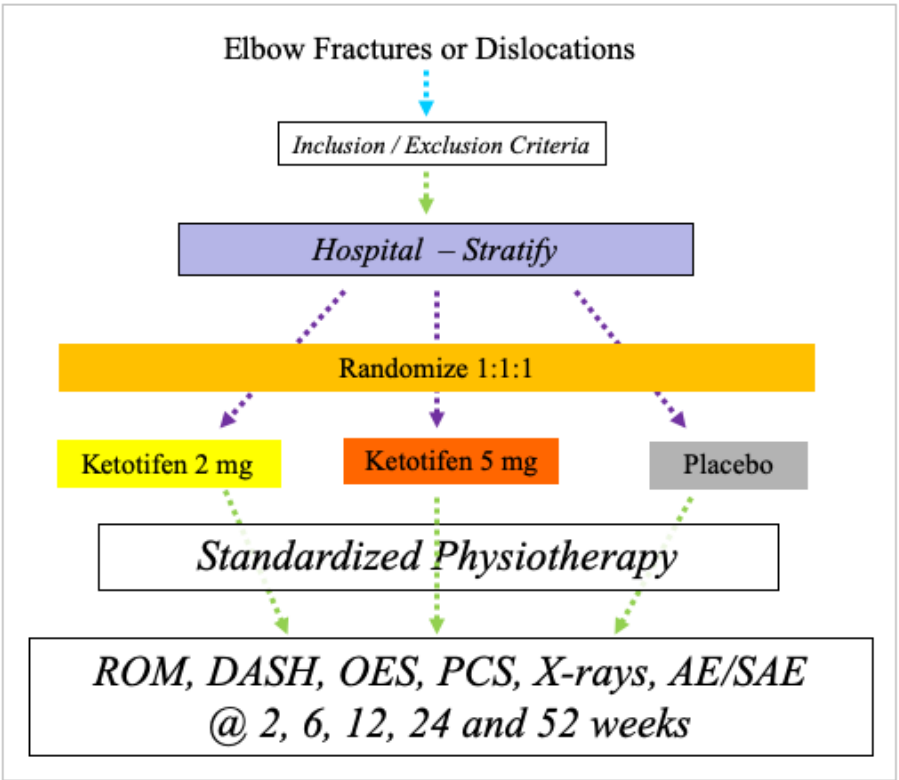
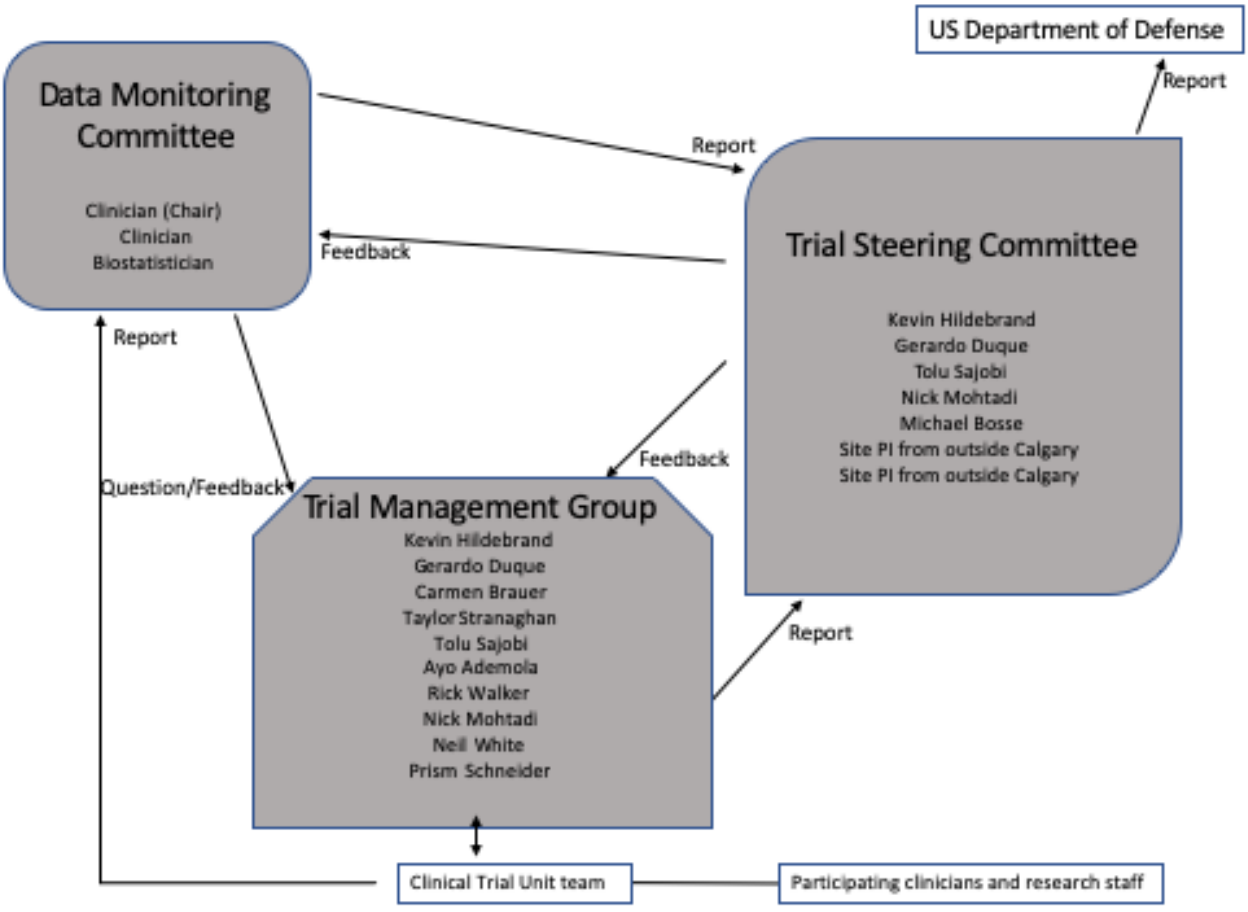


Figure 2: Relationship of trial committees



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 1.0, dated 23/Jun/2019
	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.

PERK 2: Ketotifen to prevent contractures

PrEvention of posttraumatic contractuRes with Ketotifen 2

NCT03582176

Trial Steering Committee Charter

Version 1.0, June 23, 2019

(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:	23-Jun-2019
Prepared by			
Name:	Kevin Hildebrand	Role:	Chief Investigator
Signature:		Date:	23-Jun-2019

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 [1]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 – non Calgary Site Principal Investigator (3) Tolu Sajobi – Biostatistician (4) Kevin Hildebrand – Chief Investigator (5) Gerardo Duque – Clinical Trials Unit, Facilitator (6) TBA – non Calgary Site Principal Investigator (7) TBA - non Calgary Site Principal Investigator
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 two non Calgary 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 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 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	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 people who will see the accumulating data and interim analysis by randomised group	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.
Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	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.
To whom the TSC will communicate the decisions that are made	(See Section 9)
What will happen to the papers after the meeting	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 MRC 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	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
The role of formal statistical methods	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.
How decisions or recommendations will be reached within the TSC	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.
When the TSC is quorate for decision-making	At least two non Calgary members, 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.
Any specific issues relating to the trial design that might influence the proceedings	(See Section 3)

CONTENT	DETAILS OF TSC
9. Reporting	
To whom will the TSC report their recommendations/decisions, and in what form	The TSC will report their decisions (via the Facilitator) within 3 weeks of meting 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.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	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.
What will be done if there is disagreement between the TSC and other trial committees	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 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.
The information about the TSC that will be included in published trial reports	TSC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.
Any constraints on TSC members divulging information about their deliberations after the trial has been published	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
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
TMG	Trial Management Group
TSC	Trial Steering Committee
US	United States

Figure 1: Diagram summarizing trial

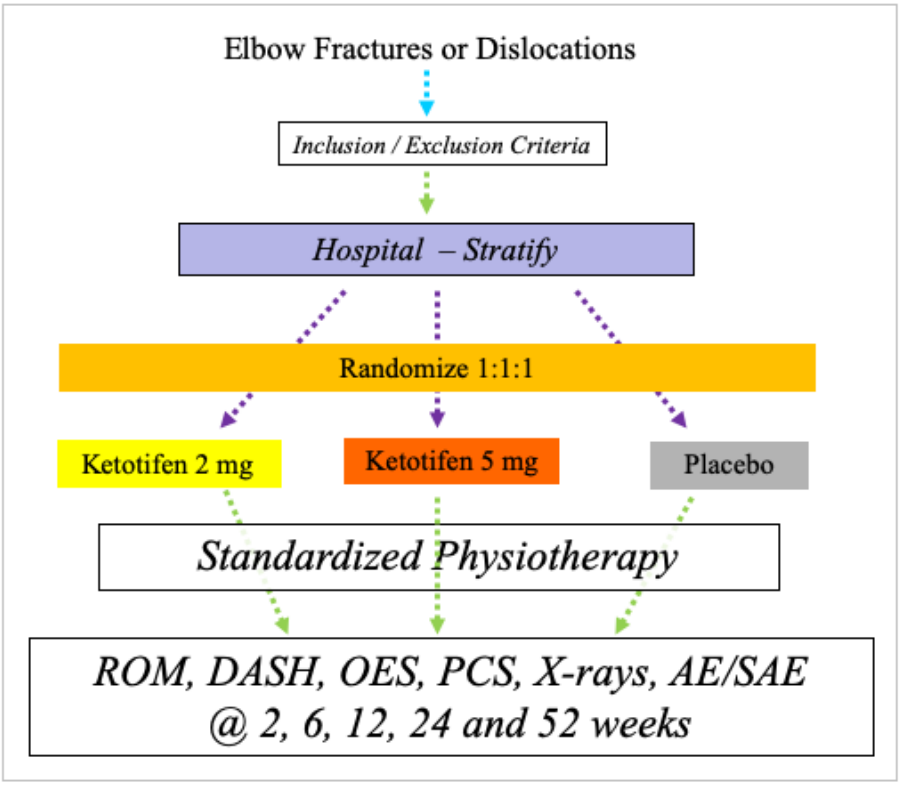
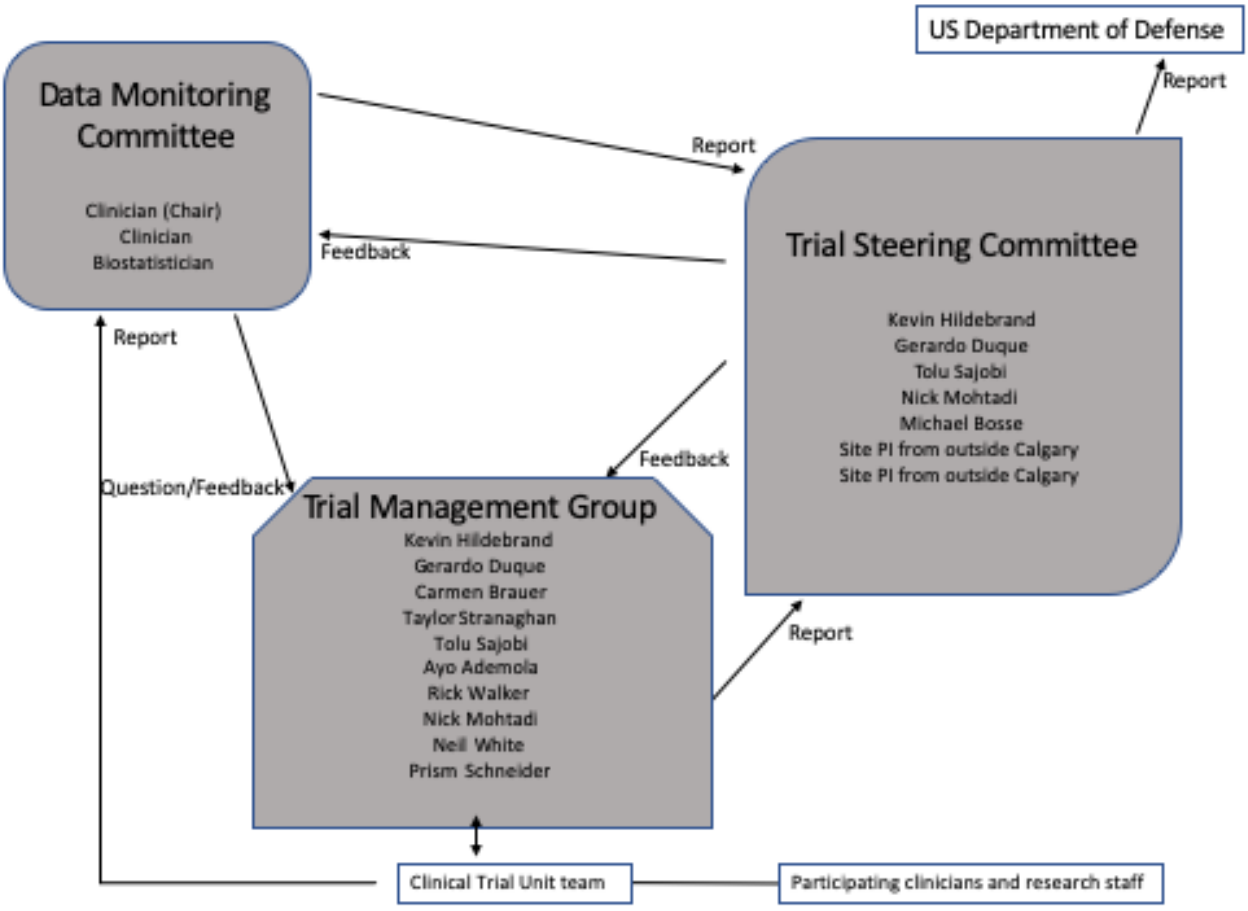


Figure 2: Relationship of trial committees



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 1.0, dated 23/Jun/2019
	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

Annexe 2: Agreement and confidentiality agreement for observers

PERK 2 (NCT03582176): Agreement to attend the Trial Steering Committee and treat all information confidentially

Please complete the following document and return to the Facilitator.

(please initial box to agree)

	I have received a copy of the TSC Charter version 1.0, dated 23/Jun/2019
	I agree to attend the Trial Steering Committee meeting on ___/____/_____
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

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

Annexe 3: Summarise changes from previous version

Version 1.0

This is version 1.0 of the TSC charter for this trial. There are no changes to be reported.

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

Alberta Health Services

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PERK 2

PERK 2 Trial Management Group Meeting #2
May 16, 2019, 4:00 – 5:30 PM
HRIC 3A14, Cumming School of Medicine, University of Calgary

Attendees: Kevin Hildebrand, Alex Garven, Taylor Stranaghan, Prism Schneider, Rick Walker, Ayo Ademola all in person
Teleconference: Tolu Sajobi
Regrets: Nick Mohtadi, Neil White

Meeting start: 4:05 PM

The agenda circulated and minutes January 16, 2019 were approved without changes.

1. Trial start

   April 26, 2019 screening started at the PLC. Five have been screened, there was 1 close recruit, but the participant elected not to consent because of not want to take pills. An “offline” start has been implemented, meaning randomization is happening while data is collected on paper forms from CRU pending completion of EPICORE database and approval of an IRB amendment.

2. Coordinating Personnel update

   Alex Garven has resigned her position effective June 14, 2019. Nicole Foldessy is hired as a student casual helping with Database and training for recruitment.

3. Database, randomization, Drug flow tracking change from CRU to EPICORE

   Costs and uncertainty / arbitrariness led to seeking quotes from 2 other agencies. EPIOCORE was selected with a combination of location, costs, and seeking opinions / seeing databases in action from 3 Calgary investigators – Rheum4U, Katheryn King-Shier Faculty of Nursing, and Vamshi Kotha Department of Radiology. They have accommodated the randomization scheme for the first 90 bottles of medication in Calgary. A drug flow system, and database in REDCap that is 21 CFR compliant are in the process of development. The final contract and cost is pending with the comment it will be under $100,000 for the whole study.

4. Roll out to other sites

   Carolinas Medical Center and Sturgeon Community Hospital in St. Albert are ready. South Health Campus is awaiting HRPO approval. The Ottawa Hospitals Civic and General Sites have final IRB revisions, HRPO and contracts.Drug is already in pharmacies at the 3 Calgary sites, not at any other sites.

   Database discussion followed. The theme / consensus is that it is best to have this in place before starting at sites outside of Calgary.

5. Committees

   Feedback was received from Neil White when the Data Monitoring Committee charter was circulated. It will be circulated again. Names for DMC will be forwarded to Dr. Hildebrand.

   Templates for TMG and TSC have not been located. These charters are pending.

6. Radiographs

   Nonunion will be a clinical diagnosis made by the treating surgeon. Heterotopic Ossification will be collected by the radiologist. Dr. Walker will input the data directly into REDCap. Dr. Walker had modifications for the HO documentation which we will add to the REDCap database. Harware complications to be collected by surgeons at sites.

   Experience with PERK 1 indicates that definitions of fracture healing (Dominant fracture line, visible on at least 2 views, lucent line [can't see bone crossing line], and with SNAPU an adjudication committee for radiographs. Also, meeting of evaluators to agree on definitions.

7. Windows around clinic visit

   After discussion, the windows for the following clinic visits are: 6 ± 1 week, 12 ± 2 weeks, 24 ± 6 weeks, 52 ± 6 weeks.

8. Granularity of data collection

   There was unanimous support for narrowing meds to those of interest that could affect sedation, fracture healing, and bone health. The classes of meds are NSAID, Narcotics, Sedatives/hypnotics, Calcium-Vitamin D, Bisphosphonates. Specific generic and trade names will be in the REDCap. Similarly, there was unanimous support for adding marijuana to the list of Current Substance Use.

   There was more varied opinion about some method of documenting dosing, or at least a definition of what yes and no means. For example, alcohol is it drinking more days than not in a week? More than a certain number of drinks? How does one record binge drinking or smoking only at certain times (weddings, Christmas, etc.)? There are weekly assessment of meds for the first 6 weeks, which is from the times between visits after 6 weeks. This will need to be revisited shortly.

9. Meaningful difference in ROM for sample size calculation

   Tabled.

   Meeting adjourned: 5:45 PM

Respectfully submitted,

Kevin Hildebrand

UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

Alberta Health Services

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PERK 2

PERK 2 Trial Management Group Meeting #3
June 10, 2019, 4:00 – 5:30 PM
HRIC 3A14, Cumming School of Medicine, University of Calgary

Attendees: Kevin Hildebrand, Alex Garven, Tolu Sajobi, Taylor Stranaghan, Rick Walker, Ayo Ademola
Teleconference: Neil White
Regrets: Nick Mohtadi, Prism Schneider

Meeting start: 4:10 PM

The agenda circulated and minutes May 16, 2019 were approved without changes.

1. Coordinating Centre Personnel update

   Alex Garven's last day is June 14, 2019. The position has been posted, last date May 31. Thirty-two applicants were screened, and 3 people were short listed. All three will be interviewed June 11, 2019 by Dr. Hildebrand and Charlene Wrona from the Cumming School of Medicine Human Resources.

2. Trial Performance update

   Screening began April 26. As of June 10, 2019, 13 people were screened, 2 were approached for consent and both declined. One was concerned about the side effects of sedation and weight gain, the other apprehensive about taking medication. Exclusion criteria were injury not within 7 days (n=4), concomitant MSK or visceral injuries preventing post-op physiotherapy (n=3), subject does not speak English (n=2) and Non-operative injury (n=2). The greater number of operative vs nonoperative cases screened is unexpected from PERK 1 experience. Strategies about fast tracking referrals to next day cast clinic, determining if sign over rounds are occurring, reaching out to urgent care centres about the trial, being able to phone contact if a participant is discharged before coordinators could be seen were presented.

3. Database, randomization, Drug flow tracking change from CRU to EPICORE

   Drug flow support has been the major task here. This is finalized. REDCap is now being constructed. Final services agreement expected this week. All with EPICORE.

4. Roll out to other sites

   Three sites are close. Carolinas last step is contract signing. Sturgeon last step is AHS approval. SHC needs AHS approval. 4 other sites have IRB approval, 3 sites have submitted IRB. 6 sites have not submitted IRB. 5 other sites have submitted to HRPO, 7 other sites have completed FDA forms, 3 other sites are registered with Health Canada.

Medications are available for SHC. Medications have to be ordered for Carolinas and Sturgeon. Right now the REDCap database is not active and the TMG recommendation to delay other sites until this step is finalized will be observed.

A session has been scheduled at the COA meeting in Montreal June 20 for site training. The plan is to introduce the Drug tracking system and REDCap database.

5. Committees

   DMC: No further changes were received. Dr. Sajobi has invited one statistician.
   TMG and TSC charters are pending.

6. Radiographs

   Various models were discussed – adjudication committee, a second evaluator reviewing a selected percentage for confirmation. In the end, several issues were presented and using the PERK 1 data will help define and clarify the issues. Dr. Walker, Dr. Hildebrand, Dr. Schneider, Dr. White and Ayo will meet to consider study designs and issues.

7. Protocol Paper

   Ayo and Dr. Hildebrand have had discussions outlining the paper. Sample size calculations, range of motion, MCID, error of measurement, modelling and subgroup analysis were discussed.

Meeting adjourned: 5:40 PM

Respectfully submitted,

Kevin Hildebrand

Subject: Re: Order request for Ketotifen manufacture
Date: Wednesday, June 26, 2019 at 9:02:22 AM Mountain Daylight Time
From: Kevin A. Hildebrand
To: Nagorski, Marlena
CC: Taylor Stranaghan, Lily Yushko
Attachments: image001.png, image002.jpg, image003.png

Thanks Marlena

From: "Nagorski, Marlena" <nagorski@barl.ca>
Date: Wednesday, June 26, 2019 at 8:59 AM
To: Kevin Hildebrand <hildebrk@ucalgary.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>, Lily Yushko <lyushko@ualberta.ca>
Subject: RE: PERK II - Marlena Notice of Vacation

Thank you. I will place the order today, and get us an ETA.

Best,
Marlena

From: Kevin A. Hildebrand <hildebrk@ucalgary.ca>
Sent: Wednesday, June 26, 2019 10:56 AM
To: Nagorski, Marlena <nagorski@barl.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>; Lily Yushko <lyushko@ualberta.ca>
Subject: Re: PERK II - Marlena Notice of Vacation

[EXTERNAL EMAIL]

18 bottles for each of the 14 sites

From: Kevin Hildebrand <hildebrk@ucalgary.ca>
Date: Wednesday, June 26, 2019 at 8:55 AM
To: "Nagorski, Marlena" <nagorski@barl.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>, Lily Yushko <lyushko@ualberta.ca>
Subject: Re: PERK II - Marlena Notice of Vacation

I would say 14 sites by the end of the year Marlena.

Kevin

From: "Nagorski, Marlena" <nagorski@barl.ca>
Date: Wednesday, June 26, 2019 at 8:52 AM
To: Kevin Hildebrand <hildebrk@ucalgary.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>, Lily Yushko

<lyushko@ualberta.ca>
Subject: RE: PERK II - Marlena Notice of Vacation

Good Morning Dr. Hildebrand,

As mentioned earlier, we will need to order the TEVA immediately. I just need the quantity to order and the go ahead from your team. How many sites will be starting up by the end of the year (assuming 18 bottles per site with 6 per each arm) plus possible re-supply for higher enrolling sites? If you can provide an estimate I can order the Teva Zaditen based on that.

Thanks,
Marlena

From: Kevin A. Hildebrand <hildebrk@ucalgary.ca>
Sent: Wednesday, June 26, 2019 10:47 AM
To: Nagorski, Marlena <nagorski@barl.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>; Lily Yushko <lyushko@ualberta.ca>
Subject: Re: PERK II - Marlena Notice of Vacation

[EXTERNAL EMAIL]

Marlena thanks for letting us know. I am ready to order the first 18 medications according to the randomization list for Sturgeon Community Hospital – site 13.

How do you do the ordering in terms of quantity? The next one imminent is Carolinas. I expect the other sites will come on over the next 3 months. If it is easier to speak, given me a call at 403 819-4985.

Kevin

From: "Nagorski, Marlena" <nagorski@barl.ca>
Date: Tuesday, June 25, 2019 at 11:52 AM
To: Kevin Hildebrand <hildebrk@ucalgary.ca>
Cc: Taylor Stranaghan <Taylor.Stranaghan@albertahealthservices.ca>
Subject: PERK II - Marlena Notice of Vacation

Good Afternoon Dr. Hildebrand,

I just wanted to let you and your team know I will be on vacation from July1-5th. Please let me know if you will require anything urgent at that time. Otherwise I will be back on the 8th.

Thanks,
Marlena

Marlena Nagorski, Hons.B.A
Clinical Trial Coordinator
Bay Area Research Logistics
Tel: 905-527-1938 Ext: 31 Fax: 905-527-1196
nagorski@barl.ca www.bayarearesearchlogistics.com

Check out the latest on our blog: 3 Steps for a More Sustainable Supply Chain

CONFIDENTIALITY Dissemination, distribution or copying of this email or the information herein by anyone other than the intended recipient, or an employee or agent of a system responsible for delivering the message to the intended recipient, is prohibited. If you are not the intended recipient, please inform the sender and delete all copies.

Subject: Re: PERK II testing
Date: Friday, June 28, 2019 at 9:48:00 PM Mountain Daylight Time
From: Kevin A. Hildebrand
To: Lily Yushko
Attachments: Database comments 20190628.docx

Hi Lily,

See the attached file.

Kevin

From: Lily Yushko <lyushko@ualberta.ca>
Date: Friday, June 28, 2019 at 10:43 AM
To: Kevin Hildebrand <hildebrk@ucalgary.ca>
Subject: PERK II testing

Hi Kevin,

Just wanted to let you know that I posted more updates to the database. You can now randomize and test NEW patients
The updates include:
- All changes/corrections from your last testing with the exception of images and new classification
- Meds form for each follow up type
- AE forms for each follow up type
- re operative report form as repeated instrument irganized by date of re operation

Outstanding are:
Protocol deviation
Protocol violation
Participant withdrawal
Radiographic
DASH
PCS
OES

Im in a meeting the whole afternoon and it might be better if we talk on Tuesday after you had a chance to review.
Please let me know,

Happy Canada Day!

Lily

Lily Yushko | **Systems Analyst, Team Lead**
Clinical Research Informatics
EPICORE Centre, Faculty of Medicine and Dentistry

362 HMRC
University of Alberta
t: 780.492.4803 f: 780.492.6059
lily.yushko@ualberta.ca
https://www.epicore.ualberta.ca/home/

Epidemiology Coordinating and Research (EPICORE) Centre
362 HMRC
University of Alberta
Edmonton AB, Canada T6G 2C2

Phone Number: 780-492-8525 or 1-877-876-9888
Fax Number: 780-492-6059 or 1-888-215-5474

Project Sign Off Form

Project Title	PERK 2: PrEvention of posttaumatic joint contactuRes with Ketotifen 2
	Database designed for this project has been reviewed in detail and meet the criteria outlined in the protocol. The database accepted as whole and complete. I understand that subsequent changes to the project will result in revisions to the database and in additional charges. I also understand that changes may cause delay and may result in inconsistent or incomplete data.
Project Coordinator	Gerardo Duque GERARDO DUQUE Printed Name Signature 2019/August/12 Date
Principal Investigator	Dr. Kevin A. Hilderbrand Kevin Hildebrand Printed Name Signature 2019/August/12 Date

Imaging Charter
PERK2

Effective Date:
15/10/2018

This Imaging Charter belongs to the Calgary Image Processing and Analysis Centre (CIPAC); it is strictly confidential and intended for internal and clinical research use in the PERK2 trial only. Prior to using this document, confirm the validation and current version number. This can be verified by requesting confirmation from the CIPAC Manager.

Individuals requesting documentation must have authorization to obtain this document, and it is their responsibility to ensure the document is properly handled.

1. Rationale

Transfer of imaging data from the point of origin at an external site to its final destination in a curated Primary Database is essential for the success of the PERK2 research study. It is the aim of the core lab to facilitate this transfer by the most efficient, consistent and user-friendly means possible. Below, the requirements and process of this transfer are described, as to reduce potential sources of error.

2. Study Setup

All imaging data that complies with the PERK2 protocol is to be sent to the core lab employed by the PERK2 study. The Calgary Image Processing and Analysis Centre (CIPAC) will act as the core lab for the duration of the project. CIPAC is a facility created to support the analysis and data management demands of medical imaging research and will be responsible for managing and supporting all external sites in their data transfers.

A diagram of the imaging data flow from point of creation at the external site to the final destination in an imaging database for visualization and analysis is depicted in Fig. 1. CIPAC personnel will be responsible for creating all required data shares and granting user access to the servers as part of the study setup. Check List 01 is used to document the shares created and is filed in section 3 of the CIPAC PERK2 regulatory binder.

Upon research ethics board approval at each site, the principal investigator (PI) should provide contact information for the data manager at their site. Core lab personnel at CIPAC will then initiate contact with the site, setting up a secure pipeline for data upload, together with user accounts, passwords, and training manuals. Any issues during connection setup will be resolved in a timely manner, and may require involvement of local IT departments for software compatibility. Documentation of each connection and all relevant communication with external sites by the core lab are documented in section 5 of CIPAC PERK2 regulatory binder. These processes, including setup of usernames and passwords for these connections will be governed by CIPAC Standards STD-01, STD-02 and STD-04, Procedures SOP-DIT-01, SOP-DIT-02 and Check List-01 and Check List-02.

© CIPAC 2014

3. Mode of Transfer

The preferred method of transfer to the core lab is through electronic upload to a pre-determined secure file transfer protocol (FTP) server, the data aggregation point for the study. There are no significant technological requirements for end users to upload data to the secure FTP server. Access to the server can be accomplished from a regular computer workstation with an internet connection and using either an FTP client (e.g., Filezilla or Cyberduck), or through an Internet browser (Chrome, FireFox, Internet Explorer, Safari etc.). Some clarification on browser and Java version employed may be required at initial site setup.

The external site data manager is not required to have technical knowledge in imaging or IT, although a minimal understanding of medical imaging and PERK2 protocol requirements will be needed. External site IT groups may be contacted if a site is unable to connect to the FTP server due to internal policies and security safeguards (e.g., firewall rules). In these cases, the external site personnel will contact their own IT group and CIPAC personnel will assist in providing relevant information to resolve connectivity issues.

Data transfer processes are supported by CIPAC STD-04, CIPAC QuickGuides for the PERK2 trial.

4. Imaging Data De-Identification and Required Imaging Data

CIPAC has adopted the CIHR and IHE's definition of de-identification as the processes that reduces the probability of an individual being associated with that individual's data. CIPAC will accept, store and release only de-identified imaging data. The extent of de-identification of imaging data and a listing of demographic information (*i.e.*, direct or indirect identifiers) that are to be preserved are detailed in the protocol and must have corresponding Research Ethics Board approval.

All users from external sites are responsible for obtaining de-identified imaging data from their imaging departments before uploading it to the FTP server. It is essential that each external site removes all subject identifiable information according to the PERK2 protocol, and replaces these identifiers with correct research identifiers. For the purposes of the PERK2 study, research identifier formats are as follows: Patient ID = Patient Name = PERK2- XX-YYYY where XX is the two-digit site number and YYYY is the four-digit subject number at each site. Each site is responsible to ensure that they have transferred the correct imaging data as per the study protocol, together with the correct timepoint labels.

If the external site is unable to provide de-identified imaging data, the external site data manager shall contact the core lab manager to determine the best course of action.

All serial radiographs acquired in the first 52 weeks following subject presentation (fracture) is to be sent to CIPAC, as per the PERK2 protocol. All imaging should be compiled in a compressed file, labeled with the Subject ID, and located on the computer workstation of the data manager. This will ensure an efficient and reliable upload process.

5. Data Curation and Corrections

Imaging data from external sites will be transferred to CIPAC by uploading to the aggregation point, the secure FTP server, via either a web-client or FTP client application. The process for these transfers is outlined in the PERK2 Quick Guides.

© CIPAC 2014

From the aggregation point, data will be downloaded by CIPAC personnel to the CIPAC data curation workstation. Data will be handled and curated according to the PERK2 protocol, and outlined by CIPAC SOP-DIT-09. The date of fracture and date of surgery, together with dates of all follow-up appointments are recorded in iDF. Timepoint labels will be added to the metadata of the imaging files by CIPAC. If an error is discovered in any portion of the de-identification (confirmed by the site) or curation (confirmed by CIPAC) of data, all relevant communication with the site will be saved in section 5 of CIPAC PERK2 Regulatory binder.

When the data curation process has been completed, data will be pushed to the primary imaging database on CIPAC servers and noted in the Imaging Transfer Record (Form 11) file and the Database Change Record (Form 9) in Source Documents folder. Imaging data in the Primary Database will be considered source data for the PERK2 study. If an error is discovered in the Primary Database, either by personnel of the core lab, the PERK2 research team, or by communication from the site, CIPAC will follow procedures outlined in SOP-DIT-06 using Check List-04 and/or Check List 05. The Database Change Record (Form 9) will be updated accordingly.

Data will be securely stored in duplicate as outlined in CIPAC STD-05. The imaging databases will then be published for viewing on individual computer workstations for reading by other authorized members of the PERK2 study team.

6. Study Completion

CIPAC will retain all imaging data and supporting source documents for two years following the date of the last enrolled subject. All further retention requirements mandated by other authorities including, but not limited to, the study sponsor, the University of Calgary, other participating institutions, United States Department of Defense, Health Canada or the Food and Drug Administration, are the responsibility of the Principal Investigators to satisfy.

During the retention period, all study data may remain open to editing as needed. Upon confirmation of study closure, or at the request of the PI, the primary database and all source documents will be locked down. Confirmation of lock down will be given and any unlocking will only be granted by request of the PI. Check List 07 will be completed, which outlines study closeout tasks.

All documentation, including electronic and hard copy source documents and all imaging data will be transferred to a long-term storage solution following the retention period. This storage solution shall be defined by the PI and transfer will be facilitated by CIPAC personnel.

7. Security

All servers used for the PERK2 study are within the Alberta Health Services (AHS) or the University of Calgary networks and reside within their respective data centres protected by their respective firewalls. CIPAC abides by policies governing these data centres and complies with the operational best practices of each entity. Note that CIPAC personnel have no control over firewalls or network setup or changes. CIPAC is responsible for reporting any issues related to the servers in each network to AHS and the University of Calgary IT Departments. CIPAC is also subject to monitoring and audits by each entity as outlined in CIPAC STD-06.

CIPAC is responsible for managing and monitoring user access to its IT and physical infrastructure. Data security measures undertaken by CIPAC are outlined in CIPAC STD-05 and STD-06.

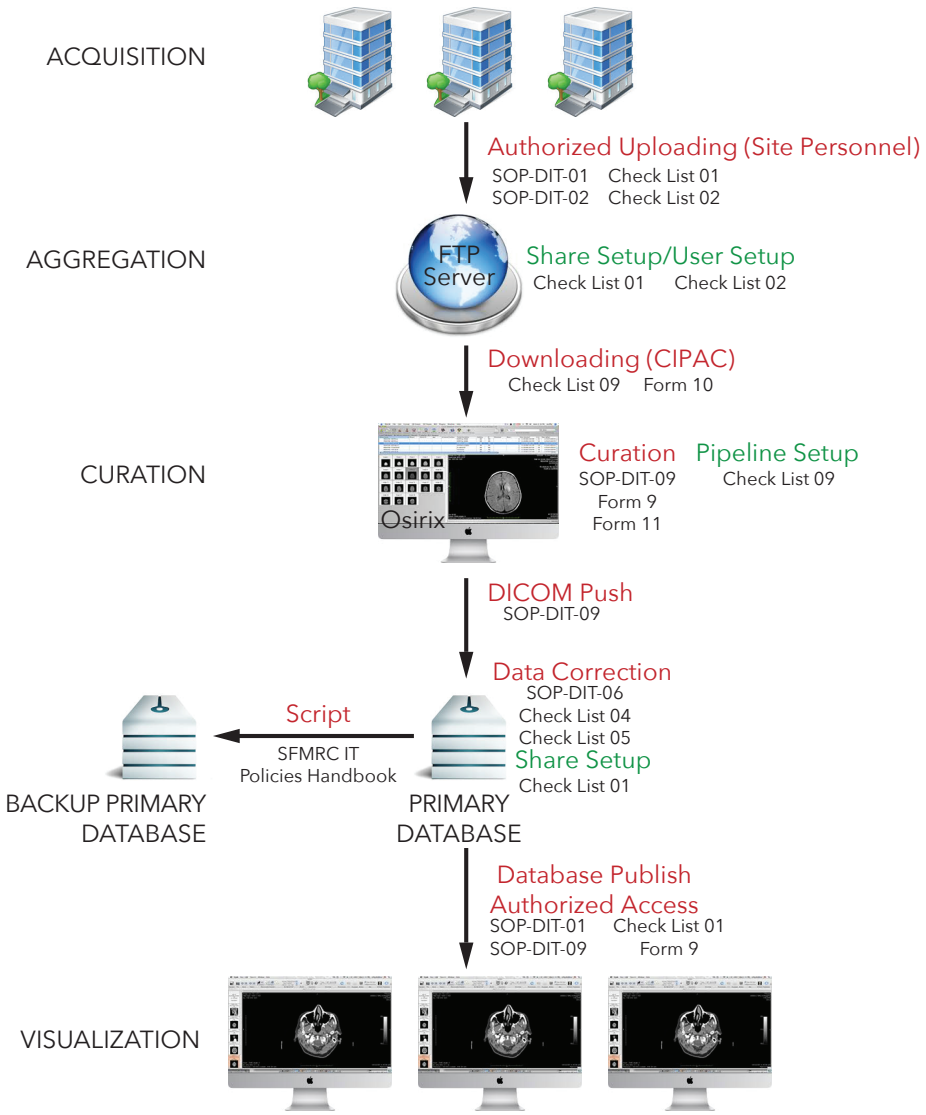
© CIPAC 2014

8. History of Approvals

Version	Date (dd/mmm/yyyy)	Printed name, Role	Signature	Description of Change
Imaging Charter v1.0	15/Oct/2018	Kevin Hildebrand, PI		First Implementation

© CIPAC 2014

Figure 1: Imaging Data Flow



PERK2 Data Flow Diagram
With Processes

© CIPAC 2014

CIPAC Meeting Minutes

October 9, 2019

Attendees:
CIPAC Team – Dr. Marina Salluzzi, Ashley Dueck, and Nicole Blenkin

PLC Team – Taylor Stranaghan & Gerry Duque

Read Only Access to RedCap

- CIPAC team would like to have to access to RedCap in order to keep track of enrolled patients that they need to pull images for
- They need to know:
    - Imaging date – Recruitment Date (Pre-op X-rays would determine baseline)
    - Randomization date
    - Participant ID
    - Accession #'s
    - RHRN #'s
- CIPAC team can later give us access to their RedCap for image access

CIPAC Q: "When are the mandatory scans required?"

- All visits within their study window required (Enrollment, 2 W, 6W, 12W, 24W, 52W)
- If visit/scan/image is missed, coordinator (Gerry) will query site about image missing. However, CIPAC will be in contact with data manager at site for this questions first. If they do not get an answer from site, they will contact us to escalate the query

CIPAC Q: "What are the mandatory scans/views required?"

- We stated all four views ***are mandatory***
    - Exceptions may include sites who may push back on getting the "oblique" views as they are not standard of care
    - We will confirm with CIPAC which sites push back on obtaining "oblique" views. This is to make them aware of sites that may only provide two views for certain participants

CIPAC Q: "When would we start?"

- CIPAC is able to pull the images for patients already seen. This does not affect our payment done December 2018
- They've agreed to a grace period. The payment already done will cover for work done through 2020

Pulling X-rays from AHS and non AHS locations

- **For AHS participants**: We would provide the information outlined above to CIPAC and they would use it to pull images into their system. They would still have a contact person at the sites in case they have questions
- **For non AHS participants**: CIPAC would contact the data manager at the site, train them on the CIPAC web portal, and then upload images following CIPAC instructions.
    - **CIPAC does not receive images in external drives/CD's**
    - **Setting up the web portal process at sites is already included in the payment done. No extra charge for this process**

CIPAC Web Based Portal

- Taylor will add instructions to SIV training. CIPAC will contact data managers at all sites to provide training
- Web Based Portal procedures are quick and simple
    - Images can upload after each patient visit, or can be don't in batches (i.e. After 12W completed.)
    - A reminder could be set up on RedCap to start the upload process at 12W for patients

Future Meetings

- Purpose: CIPAC to update us on site status and address questions/concerns with imaging at each site
- They can meet in-person or it can be done through email updates

Calgary Image Processing and Analysis Centre

Foothills Medical Centre – South Tower Room 1105
1403 29 Street NW, Calgary, AB T2N 4Z6
Telephone: 403 944 3632
Fax: 403 944 5380
Email: msalluzz@ucalgary.ca

November 22, 2016

Dr. Kevin A. Hildebrand
Bone and Health Joint Program
Department of Surgery
University of Calgary
3280 Hospital Drive NW
Calgary, AB T2N 4Z6

Dear Dr. Hildebrand:

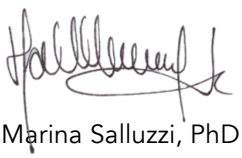
RE: Letter of Support

I am pleased to write you this letter of support for the trial *Prevention of post-traumatic contractures with Ketotifen II (PERK II)* submitted to the Department of Defense. The Calgary Image Processing and Analysis Centre (CIPAC) has been accomplishing data aggregation, curation, secure storage and transfer of imaging data for research programs for over five years. We have built a strong relationship with Alberta Health Services (AHS) Privacy and Diagnostic Imaging departments that has led to multiple shared services and have been providing services to investigators at the University of Calgary with national and international studies, including the ESCAPE, NAVIGATE, SPECTRA and MAP-IT trials, among others.

Your project involves accessing clinical digital x-ray scans of consenting participants. We can assist you with the process of requesting data, re-identification and transfer to your laboratory for analysis and aggregating data from external sites for secure storage here in Calgary. CIPAC will have a technical person available to assist with setup of all data management processes and will provide consistently anonymized data from AHS and up to 10 external sites. The data will be stored in a secure environment for further analysis by your research team. CIPAC personnel will be responsible for all data management, including data curation and external site connection and support; access to your team members will be provided upon your request or approval only. We estimate a cost of $90 per subject enrolled in your study (see below for details). You will be required to obtain ethics approval for this study, as well as establish a research agreement with AHS (to access the data collected in Alberta) and with other researchers participating in your study.

I look forward to working with you on this project and extending our collaboration into the future.

Sincerely,



Marina Salluzzi, PhD
Manager, CIPAC

Assumptions:

702 subjects
4 x-ray scans per subject
External Sites: 10
In-Province Sites: 5
Data storage in AHS
Length of the study: 4 years
Retention period: 2 year upon completion of the study

Quote:

Service	Year 1	Year 2	Year 3	Year 4	TOTAL
Trial Set Up	$8,370	-	-	-	$8,370
Data Management	$2,085	$4,729	$5,369	$6,949	$19,132
Support	$6,000	$8,033	$8,059	$8,072	$30,164
Administrative	$1,645	$1,276	$1,343	$1,502	$5,767
TOTAL/YEAR	$18,100	$14,039	$14,771	$16,523	$63,433
Cost per patient	$90.36				

A Comparison of Frequentist and Bayesian Power Analyses for Non-Inferiority Trials Designs

Ayoola Ademola[1], Bijoy Menon[1,2], Michael D. Hill[1,2], Lehana Thabane[3], Kevin Hildebrand[4], Tolulope Sajobi[1,2]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada

[2]Department of Clinical Neurosciences, University of Calgary, Calgary, Canada

[3]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

[4]Department of Surgery, University of Calgary, Calgary, Canada

Purpose: Non-inferiority trial designs are commonly used to examine whether a new experimental treatment is not unacceptably less efficacious than another treatment (i.e., control) already in use. This study compares frequentist and Bayesian approaches to power analysis for non-inferiority clinical trials design with binary endpoints.

Method: Monte Carlo Markov Chain Bayesian simulation with beta prior distribution was conducted to examine the impact of group size ratio (1:1, 1:3), treatment effect difference (3% - 9%), prior distribution, sample size (N = 750, 1000, 1600), and non-inferiority margin on Bayesian and frequentist approaches to sample size estimation non-inferiority trials. The estimated statistical power was compared to the frequentist power calculation for each of the simulated conditions.

Results: Preliminary findings show that there were negligible differences in the estimated statistical power for the frequentist approach and the Bayesian model with non-informative prior, regardless of the sample size and anticipated treatment effect sizes. For equal group size ratio condition, the Bayesian model resulted in reduced statistical power than the frequentist approach when the strength of prior belief favors the existing treatment (i.e., control). But the former resulted about 5% higher statistical power than the latter when the strength of prior belief favours the new treatment. Overall, the stronger the belief in group with higher proportion of the outcome, the higher the statistical power, regardless of the group size ratio, anticipated treatment effect differences, and sample size.

Conclusion: Bayesian power analysis for non-inferiority trials can result in increased statistical power (for a smaller sample size) than the frequentist approach when there is stronger prior evidence of the efficacy of one treatment over the other. Bayesian power analyses can yield optimal sample size required compared to the conventional frequentist approach when there is stronger evidence from literature or historical data to inform the prior distribution.

Deleted: McCaig Institute for Bone and Joint Health

Deleted: if

Commented [KAH1]: What are the types of "prior distribution"? earlier in the sentence "beta prior distribution" was mentioned. Will the types of prior distribution, or maybe prior distribution and no prior distribution in the simulations, be evident to a statistical audience?

Deleted: our

Deleted: than

A Differential Item Functioning Analysis of the DASH Outcome Measure in a Randomized Controlled Trial of Patients with Elbow Fractures

Tolulope Sajobi[1], Ayoola Ademola[1], Prism Schneider[1,2], Stephanie Yee[2], Alexandra Garven[2], Richard Walker[3], & Kevin Hildebrand[2]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada
[2]Department of Surgery & McCaig Institute for Bone & Joint Health, University of Calgary, Calgary, Canada
[3]Department of Radiology, University of Calgary, Calgary, Canada

Abstract

Background: Patient-reported outcomes measures (PROMs), such as the Disabilities of the Arm, Shoulder and Hand (DASH), are commonly used as endpoints in orthopaedic trials. Meaningful group comparisons of PROMs scores across treatment groups require that these measures are free from bias due to factors unrelated to patients' health, i.e., free from differential item functioning (DIF). The objectives of the study are to investigate the presence of DIF in DASH and to compare DIF-adjusted DASH scores to unadjusted scores in patients with elbow fractures or dislocations.

Methods: Data are from the PrEvention of Posttraumatic Joint contractuRes With Ketotifen I (PERK I), a randomized controlled trial that compares the efficacy of oral ketotifen over a lactose placebo in reducing joint contracture severity in adult patients with isolated elbow fractures and/or dislocations. The degree of disability in the elbow was assessed using the 30-item DASH questionnaires at each follow-up timepoint. An hybrid ordinal logistic regression was used to test for both uniform and non-uniform DIF in the baseline patient-reported DASH scores across sex, and age groups (< 50 years, >50 years). Differences in Nagelkerke R^2 were used to assess magnitude of the DIF effect sizes. A three-parameter graded response model (GRM) was fitted to the data and the estimated model parameters were used to derive DIF-adjusted overall DASH scores.

Results: Of the 108 patients included in this analysis, 55(50.9%) were males and 49(45.4%) were older than 50 years. Six DASH items exhibited non-uniform DIF with respect to sex with DIF effect sizes ranging between 0.01 and 0.05. Similarly, 4 items that exhibited non-uniform DIF with respect to age, with DIF effect sizes that range between 0.03 and 0.09. Results from the GRM shows that accounting for DIF led to slightly lower DASH scores for older patients and slightly higher scores for younger patients. For patients with higher DASH scores, accounting for DIF led to slightly higher scores, regardless of the sex.

Conclusions: Sex and age differences are significantly associated with DIF bias in patient-reported DASH items. Psychometric analyses of PROMs used in clinical trials are recommended as sensitivity analysis for the trials' primary analysis and other planned subgroup analyses.

Subject: FW: SCT Annual Meeeting Abstract Notification
Date: Thursday, February 28, 2019 at 6:58:28 PM Mountain Standard Time
From: Ayoola Ademola
To: Michael D. Hill, ThabanL@mcmaster.ca, Kevin A. Hildebrand, Bijoy.Menon@albertahealthservices.ca
CC: Tolulope Sajobi
Attachments: image001.jpg

Sirs,

I am glad to inform you that our abstract submitted to Society for Clinical Trials has been accepted for oral presentation at the annual meeting in New Orleans.

Thanks

From: Mary Keller <mkeller@fernley.com>
Sent: February 27, 2019 1:44 PM
To: Ayoola Ademola <ayoola.ademola@ucalgary.ca>
Subject: SCT Annual Meeeting Abstract Notification

CAUTION: This Email is External.

SCT
SOCIETY FOR CLINICAL TRIALS

February 27, 2019

Dear Ayoola Ademola,

Congratulations! The SCT Program Committee has accepted your abstract "**A Comparison of Frequentist and Bayesian Power Analyses for Non-Inferiority Trials Designs**" for **oral presentation** in a Contributed Paper Session at the 40th Annual Meeting of the Society for Clinical Trials. The meeting will take place May 19-22, 2019 at the SHERATON NEW ORLEANS HOTEL, in New Orleans, LA.

Please respond to this email with confirmation that you will be presenting at the 2019 meeting no later than March 4, 2019.

PRESENTATION
The abstracts that have been accepted for presentation at the meeting will be slotted into the on-line Program on the SCT Meeting website and will include the date, time and room number for your session. Once all sessions have been slotted, we will notify you and provide a link to the Program. **Please note:** The

Program will be subject to change so please make sure to check for your session once you have been notified. Each program participant will be allotted a total of 15 minutes for presentation. Of this, 10 minutes is designated for lecture and 5 minutes is reserved for a question and answer discussion period. All presentation rooms will be equipped with a lectern, microphone, LCD projector (for PowerPoint® presentation) and a laptop computer. No other audiovisual equipment will be available. Please bring your presentation saved to a flash drive which you will upload to the laptop in your presentation room prior to the start of the session. Please plan to arrive to your session room a few minutes early to load your presentation to the laptop.

REGISTRATION
All presenting authors are required to register for the meeting. You must be registered for the meeting by March 15, 2019 in order to make your presentation. The conference registration fee for SCT members who register by the March 15, 2019 early bird deadline is $550 US dollars. The early bird conference registration fee for Non-Members is $750 US dollars. After March 15, 2019, registration fees increase by $100 US dollars. Be sure to register prior to the early bird deadline to lock in the discounted rate. Students receive a discounted registration fee of $150 US dollars for members and $225 US dollars for non-members, with student identification. **Online registration is available.**

VERIFICATION OF INFORMATION
Your name, abstract title and affiliation will be printed in the SCT program book as they appear below. If there are any changes please notify the Society in writing so that this information will appear correctly in the final program.

Presenter Name: **Ayoola Ademola**
Abstract Title: **A Comparison of Frequentist and Bayesian Power Analyses for Non-Inferiority Trials Designs**
Affiliation: **University of Calgary**

Changes or updates may be sent via email to mkeller@fernley.com. Additionally, if there are unfortunate circumstances which result in you being unable to present your abstract, please notify us via email no later than March 31, 2018.

Once again, congratulations, and we look forward to seeing you in New Orleans.

Sincerely,
Mary Keller
SCT Associate Director

100 N. 20th Street, Suite 200 • Philadelphia, PA 19103 USA
Telephone: +1 215-320-3878 • Fax: +1 215-564-2175 • Web: http://www.sctweb.org • E-mail: sct@fernley.com

CAUTION: External Email This Email originated from outside the University of Calgary. Please exercise caution when opening attachments, clicking on links or when asked to enter usernames/passwords. Report suspicious emails to "reportphishing@ucalgary.ca" or via the Junk Email Reporting Tool in the Outlook Tool Bar. **For More Information call the Service Desk.**

Session Details

A COMPARISON OF FREQUENTIST AND BAYESIAN POWER ANALYSES FOR NON-INFERIORITY TRIALS DESIGNS

Ayoola Ademola

Session Type: Contributed Paper Session - Oral Presentation

Keyword Categories: Trial Design
Statistical Analysis
Choosing interventions

Author(s): Ayoola . Ademola (University of Calgary)
Bijoy K Menon (1) Department of Community Health Sciences (2) Department of Clinical Neurosciences, University of Calgary)
Michael D. Hill (1) Department of Community Health Sciences (2) Department of Clinical Neurosciences, University of Calgary)
Lehana Thabane (Department of Health Research Methods, Evidence and Impact, McMaster University)
Kevin Hildebrand (Department of Surgery, University of Calgary)
Tolulope Sajobi (1) Department of Community Health Sciences (2) Department of Clinical Neurosciences, University of Calgary)
Arpita Chatterjee (Georgia Southern University)

Session Description:

Purpose: Non-inferiority trial designs are commonly used to examine whether a new experimental treatment is non-inferior (not unacceptably less efficacious) than another treatment (i.e., control). This study compares Frequentist and Bayesian approaches to power analysis for non-inferiority clinical trials design with binary endpoints.

Method: Monte Carlo Markov Chain Bayesian simulation with beta prior distribution was conducted to examine the impact of group size ratio (1:1, 1:3), treatment effect difference (3% - 9%), prior distribution (beta distributions; a = [0.40:60], b= [0.60:0.40]), sample size (N = 750, 1000, 1600), and non-inferiority margin (NI margin = 5%, 7%, 10%) on Bayesian and Frequentist approaches to sample size estimation in non-inferiority trials. The estimated statistical power was compared to the Frequentist power calculation for each of the simulated conditions.

Results: Preliminary findings show that there were negligible differences in the estimated statistical power for the Frequentist approach and the Bayesian model with non-informative prior, regardless of the sample size and anticipated treatment effect sizes. For equal group size ratio condition, the Bayesian model resulted in reduced statistical power than the Frequentist approach when the strength of prior belief favors the existing treatment (i.e., control). The former resulted in about 5% higher statistical power than the latter when the strength of prior belief favours the new treatment. Also, the statistical power for both approaches increased as the NI margin increased. Overall, the stronger the belief in active treatment, the higher the statistical power, regardless of the group size ratio, anticipated treatment effect differences, and sample size and NI margin.

Conclusion: Bayesian power analysis for non-inferiority trials can result in increased statistical power (for a smaller sample size)

Conclusion: Bayesian power analysis for non-inferiority trials can result in increased statistical power (for a smaller sample size) and optimal sample size than the Frequentist approach when there is stronger prior evidence of the efficacy of the active treatment over the control and larger NI margin. The choice of NI margin and prior distribution (belief) in Bayesian analysis should be guided by clinical evidence from literature.

Subject: Fw: SCT Annual Meeeting Abstract Notification
Date: Thursday, February 28, 2019 at 5:04:54 PM Mountain Standard Time
From: Tolulope Sajobi
To: Kevin A. Hildebrand, Prism Schneider, Ayoola Ademola, Alexandra Garven, Stephanie Yee, Richard Edward Allan Walker
Attachments: image001.jpg

Hi Everyone,

Our abstract has been accepted for oral presentation at the annual meeting of the Society for Clinical Trials in New Orleans.

Tolu

From: Mary Keller <mkeller@fernley.com>
Sent: Wednesday, February 27, 2019 1:43 PM
To: Tolulope Sajobi
Subject: SCT Annual Meeeting Abstract Notification

CAUTION: This Email is External.

SCT
SOCIETY FOR CLINICAL TRIALS

February 27, 2019

Dear Tolu Sajobi,

Congratulations! The SCT Program Committee has accepted your abstract "**A Differential Item Functioning Analysis of the DASH Outcome Measure in a Randomized Controlled Trial of Patients with Elbow Fractures**" for **oral presentation** in a Contributed Paper Session at the 40th Annual Meeting of the Society for Clinical Trials. The meeting will take place May 19-22, 2019 at the SHERATON NEW ORLEANS HOTEL, in New Orleans, LA.

Please respond to this email with confirmation that you will be presenting at the 2019 meeting no later than March 4, 2019.

PRESENTATION
The abstracts that have been accepted for presentation at the meeting will be slotted into the on-line

Program on the SCT Meeting website and will include the date, time and room number for your session. Once all sessions have been slotted, we will notify you and provide a link to the Program. **Please note:** The Program will be subject to change so please make sure to check for your session once you have been notified. Each program participant will be allotted a total of 15 minutes for presentation. Of this, 10 minutes is designated for lecture and 5 minutes is reserved for a question and answer discussion period. All presentation rooms will be equipped with a lectern, microphone, LCD projector (for PowerPoint® presentation) and a laptop computer. No other audiovisual equipment will be available. Please bring your presentation saved to a flash drive which you will upload to the laptop in your presentation room prior to the start of the session. Please plan to arrive to your session room a few minutes early to load your presentation to the laptop.

REGISTRATION

All presenting authors are required to register for the meeting. You must be registered for the meeting by March 15, 2019 in order to make your presentation. The conference registration fee for SCT members who register by the March 15, 2019 early bird deadline is $550 US dollars. The early bird conference registration fee for Non-Members is $750 US dollars. After March 15, 2019, registration fees increase by $100 US dollars. Be sure to register prior to the early bird deadline to lock in the discounted rate. Students receive a discounted registration fee of $150 US dollars for members and $225 US dollars for non-members, with student identification. **Online registration is available.**

VERIFICATION OF INFORMATION

Your name, abstract title and affiliation will be printed in the SCT program book as they appear below. If there are any changes please notify the Society in writing so that this information will appear correctly in the final program.

Presenter Name: **Tolu Sajobi**
Abstract Title: **A Differential Item Functioning Analysis of the DASH Outcome Measure in a Randomized Controlled Trial of Patients with Elbow Fractures**
Affiliation: **University of Calgary**

Changes or updates may be sent via email to mkeller@fernley.com. Additionally, if there are unfortunate circumstances which result in you being unable to present your abstract, please notify us via email no later than March 31, 2018.

Once again, congratulations, and we look forward to seeing you in New Orleans.

Sincerely,
Mary Keller
SCT Associate Director

100 N. 20TH STREET, SUITE 200 • PHILADELPHIA, PA 19103 USA
TELEPHONE: +1 215-320-3878 • FAX: +1 215-564-2175 • WEB: HTTP://WWW.SCTWEB.ORG • E-MAIL: SCT@FERNLEY.COM

CAUTION: External Email This Email originated from outside the University of Calgary. Please exercise caution when opening attachments, clicking on links or when asked to enter usernames/passwords. Report suspicious emails to "reportphishing@ucalgary.ca" or via the Junk Email Reporting Tool in the Outlook Tool Bar. **For More Information call the Service Desk.**

Session Details

A DIFFERENTIAL ITEM FUNCTIONING ANALYSIS OF THE DASH OUTCOME MEASURE IN A RANDOMIZED CONTROLLED TRIAL OF PATIENTS WITH ELBOW FRACTURES

Tolu Sajobi

Session Type: Contributed Paper Session - Oral Presentation

Keyword Categories:
Outcomes
Statistical Analysis
Personalize Medicine

Author(s):
Tolu . Sajobi (University of Calgary)
Ayoola Ademola (Department of Community Health Sciences, University of Calgary)
Prism Schneider (Department of Surgery & McCaig Institute of Bone and Joint Health, University of Calgary)
Stephanie Yee (Department of Surgery & McCaig Institute for Bone and Joint Health, University of Calgary)
Alexandra Garven (Department of Surgery & McCaig Institute for Bone and Joint Health, University of Calgary)
Richard Walker (Department of Radiology, University of Calgary)
Kevin Hildebrand (Department of Surgery & McCaig Institute for Bone and Joint Health, University of Calgary)

Session Description:

Background: Patient-reported outcomes measures (PROMs), such as the Disabilities of the Arm, Shoulder and Hand (DASH), are commonly used as endpoints in orthopaedic trials. Meaningful group comparisons of PROMs scores across treatment groups require that these measures are free from bias due to factors unrelated to patients' health, i.e., free from differential item functioning (DIF). The objectives of the study are to investigate the presence of DIF in DASH and to compare DIF-adjusted DASH scores to unadjusted scores in patients with elbow fractures or dislocations.
Methods: Data are from the PrEvention of Posttraumatic Joint contractuRes With Ketotifen I (PERK I), a randomized controlled trial that compares the efficacy of oral ketotifen over a lactose placebo in reducing joint contracture severity in adult patients with isolated elbow fractures and/or dislocations. The degree of disability in the elbow was assessed using the 30-item DASH questionnaires at baseline, 12, and 52 weeks after randomization. An hybrid ordinal logistic regression was used to test for both uniform and non-uniform DIF in the baseline patient-reported DASH scores across sex, and age groups (< 50 years, >50 years). Differences in Nagelkerke R2 were used to assess magnitude of the DIF effect sizes. A three-parameter graded response model (GRM) was fitted to the data and the estimated model parameters were used to derive DIF-adjusted overall DASH scores.

Results: Of the 108 patients included in this analysis, 55(50.9%) were males and 49(45.4%) were older than 50 years. Six DASH items exhibited non-uniform DIF with respect to sex with DIF effect sizes ranging between 0.01 and 0.05. Similarly, 4 items that exhibited non-uniform DIF with respect to age, with DIF effect sizes that range between 0.03 and 0.09. Results from the GRM

shows that accounting for DIF led to slightly lower DASH scores for older patients and slightly higher scores for younger patients. For patients with higher DASH scores, accounting for DIF led to slightly higher scores, regardless of the sex.

Conclusions: Sex and age differences are significantly associated with DIF bias in patient-reported DASH items. Psychometric analyses of PROMs used in clinical trials are recommended as sensitivity analysis for the trials' primary analysis and other planned subgroup analyses.

Word Count: 362 (max = 500)

Evaluating Differential Response Patterns to Disabilities of the Arm, Shoulder, and Hand (DASH) in Patients with Elbow Contractures

Tolulope Sajobi[1], Ayoola Ademola[1], Prism Schneider[2,3], Stephanie Yee[2], Alexandra Garven[2], Richard Walker[4], Nicholas Mohtadi[2,3], & Kevin Hildebrand[2,3]

[1]Department of Community Health Sciences, University of Calgary, Calgary, Canada
[2]Department of Surgery, University of Calgary, Calgary, Canada
[3]McCaig Institute of Bone and Joint, University of Calgary, Calgary, Canada
[4]Department of Radiology, University of Calgary, Calgary

Abstract

Background: Patient-reported outcomes measures (PROMs), such as the Disabilities of the Arm, Shoulder and Hand (DASH), are commonly used as endpoints in orthopedic trials. Meaningful group comparisons of these PROMs scores across treatment groups require that patients' measures are free from bias due to factors unrelated to patients' health (i.e. free from Differential Item Functioning (DIF)). This study evaluates presence and impact of DIF in DASH for patients with elbow contractures. **Methods**: Baseline data from the PrEvention of Posttraumatic Joint contractuRes With Ketotifen I (PERK I), a pilot randomized controlled trial comparing oral Ketotifen with a lactose placebo in reducing joint contracture severity in adult patients with isolated elbow fractures and/or dislocations, was used for this analyses. Patient's perceived degree of functional disability was assessed using the 30-item DASH questionnaire. A hybrid ordinal logistic regression/2-parameter graded-response model was used to detect and adjust for uniform and non-uniform DIF in the baseline patient-reported DASH scores across sex, age groups (< 50 years, ≥50 years) and surgery status.

Results: Of the 126 patients included in this analysis, 55(50.9%) were males, 49(45.4%) were older than 50 years, and X(Y%) had surgery for the injury. About a quarter of DASH and QuickDASH items exhibited moderate uniform and non-uniform DIF with respect to sex, age, or surgery status. The DIF estimates resulted in over-estimation of sex differences in DASH scores and under-estimation of difference in DASH scores across age and surgery status subgroups.

Conclusions: Patient-reported DASH items are prone to DIF especially across sex, age, and surgery subgroups. Psychometric analyses of PROMs used in clinical trials are recommended for trial primary outcomes analysis and other planned subgroup analyses in RCTs.

Deleted: and in

Deleted: that compares the efficacy of

Deleted: over

Deleted: and

Deleted: and

1. Introduction

Patient-reported outcomes measures (PROMs), such as the Disabilities of the Arm, Shoulder, and Hand (DASH), are widely used to elicit patients' direct evaluation of their health and well-being, and are commonly used in randomized clinical trials (RCTs) to demonstrate the efficacy/effectiveness of treatment/interventions [1-3]. Several regulatory bodies such as the United States Food and Drug Administration (FDA) [4] and the European Medicines Agency [5] have promoted the use of PROMs as clinical endpoints in RCTs [4-6]. In addition to showing evidence of therapeutic benefits of treatment interventions in terms of conventional clinical outcomes such as mortality, investigators and trial sponsors are required to report treatment effects on patients' report of their health status or quality of life.

Deleted: ,

Deleted: of treatment interventions,

In order for comparisons of PROMs across population sub-groups to be accurate, a fundamental assumption is that these PROMS must be valid and reliable across population groups [7]. While PROMs used in RCTs are usually evaluated for construct validity and test-retest reliability, these tools are rarely evaluated for the effects of differential item functioning (DIF), which can also affect construct validity [8 - 9]. DIF occurs when individuals with the same underlying (i.e. latent) level of health do not interpret a measure's items in the same way [9]. DIF can result in an unexpected lack of scale comparability, biased treatment/subgroup differences, reduced statistical power, and erroneous conclusions about treatment effects [10-11].

The Disability of the Arm, Shoulder, and Hand (DASH) is a commonly used PROM for assessing disability in orthopedic patients' clinical trials studies and has undergone comprehensive psychometric evaluation

related to its validity and responsiveness in orthopedic populations [3,12-14]. However, recently published studies have expressed concerns about the construct and discriminant validity of the DASH and Quick DASH in patients with upper extremity disorders [15-17]. One potential cause of these differences in psychometric performances could be the presence of DIF. Although the presence of DIF in DASH and QuickDASH items have been previously investigated [18-20], most of these analyses have been conducted in observational designs and have not explored the potential impact of DIF on conclusions about group difference in RCTs. This study investigated the presence of DIF in DASH administered to participants of a RCT of patients with elbow fractures across sex, age, and surgical subgroups.

2. Methods

2.1 PrEvention of Posttraumatic Joint contractuRes with Ketotifen 1 (PERK 1) Trial

Data are from the PrEvention of Posttraumatic Joint contractuRes with Ketotifen 1 (PERK 1) trial, a pilot RCT using a parallel design comparing ketotifen to a lactose-placebo in a 1:1 ratio that included 148 participants [21]. Patients were randomized to receive either placebo (lactose) or Ketotifen 5 mg, administered orally twice daily for 6 weeks. The primary outcome was the range of motion (extension-flexion arc of motion) at 12 weeks. Secondary endpoints included range of motion at other time points (i.e. 6, 24 and 52 weeks), and Disability Arm, Shoulder and Hand (DASH) and the 12-item Short Form Health survey (SF12) at baseline, 6, 12, 24 and 52 weeks after randomization. The inclusion criteria were participants 18 years and old with injury less than 7 days, isolated distal humerus (AO/OTA type 13), and/or proximal ulna and/or proximal radius fractures (AO/OTA type 21) and/or elbow dislocations (open fractures with or without nerve injury). The exclusion criteria were participants with pre-existing elbow contracture, arthritis, gout, or nonspecific monoarticular arthritis of the elbow, prior injury or surgery to the affected elbow, inability to mobilize elbow within

Deleted: differential item functioning (

Deleted:)

Deleted: Phase II

Deleted: double blinded, two arms randomized clinical trial of about 150 patients with elbow fracture

Commented [KAH1]: How much of this is necessary if baseline is all that we are reporting? And do we need to mention ROM, or SF12 when the topic is the DASH only?

Deleted: Distal

Deleted: , elbow

Deleted:)

14 days of injury, oral hypoglycemic medications, lactose intolerance, female who is pregnant or breast-feeding, language or cognitive difficulties preventing questionnaire completion.

Deleted: 21

Deleted: , concomitant musculoskeletal or visceral, injuries that prevent post- operative elbow physiotherapy

Deleted: prior injury or surgery to the affected elbow, total elbow replacement planned for operative treatment,

Deleted: , severe renal impairment. Other exclusion criteria were severe hepatic impairment, history of epilepsy, male or female of reproductive age unwilling to use two effective methods of contraception

2.2 Disability of the Arm, Shoulder, and Hand (DASH)

The DASH is a 30-item patient-reported measure specifically developed to capture patients' ratings of functional disabilities in diseases of the upper extremities [12-14, 22-24]. The items ask about the severity of pain, activity-related pain, tingling, weakness and stiffness (5 items), the problem's impact on social activities, work, sleep, and self-image (4 items), and the degree of difficulty in performing different physical activities because of the arm, shoulder, or hand problem (21 items). Each item has five response options. The scores for all items are then used to calculate a scale score ranging from 0 (no disability) to 100 (most severe disability). The DASH is known to have excellent psychometric properties in disorders of upper extremities including validity, reliability, and responsiveness [25]. A shorter version of the DASH, named as the QuickDASH, has been recently developed and shown to have similar excellent psychometric properties in patients with disorders of the upper extremity [25-27].

2.3 Statistical Analysis

Commented [KAH2]: Figure 4 mentions latent score in the x-axis but I don't see a latent score mentioned in the statistics section

Mean, standard deviation, frequencies, and percentages were used to summarize patients' baseline demographic and clinical characteristics. Wilcoxon rank test and chi square test were used to test for differences among treatment groups on continuous and categorical variables, respectively. A hybrid ordinal logistic regression [28] was used to test for both uniform and non-uniform DIF in the baseline patient-reported DASH scores across sex, age groups (< 50 years, >50 years) and surgery (yes, no). Hybrid OLR/IRT, is a two-stage modeling approach that involves using a two-parameter graded response model

Deleted: t

Deleted: and

Commented [KAH3]: What are these? Abbreviations? Do they need to be spelled out?

to estimate the latent construct and an ordinal logistic regression model to test and quantify DIF in each item. These models were iteratively fitted to the data until there is no significant change in estimate latent construct after testing for DIF. For items identified with DIF, previous research studies have recommended a combination of significant likelihood ratio test (LRT) chi square statistic and change in Nagelkerke's pseudo R^2 > 3.5% for flagging non-negligible DIF effects on items [29]. Given the small sample size for this study, Monte Carlo simulations were used to determine the optimal thresholds for non-negligible DIF effect sizes for each DIF analysis, as measured by the magnitude of change in Nagelkerke's pseudo R^2, following a significant LRT chi square statistic. Finally, we examined the combined impact (scale level impact) of multiple identified items with DIF on the DASH using the differential test function (DTF) index that compared the test characteristic curves with and without DIF items. A conservative threshold based on Monte Carlo simulations assessed the magnitude of the DTF 14. All analyses were conducted in R software package [30].

3. Results

Of the 126 patients included in this analysis, 59 (47%) are females, 50 (40%) had surgery, while 2 (1%) had open elbow fractures. Patients had been categorized into two age groups: 18 to 49 years (60 of 126 [48%]) and ≥ 50 years (66 of 126 [52%]). There were no significant differences in patient-reported DASH scores across sex and age subgroups. However, patients who had elbow surgery reported significantly lower DASH scores than patients who had no surgery (Table 1).

For sex-related DIF, Monte Carlo simulations of the hybrid OLR/IRT model revealed that the optimal threshold for non-negligible DIF effect is 2.9%. Using this threshold, four DASH items were flagged for

Deleted:

Commented [KAH4]: Is DTF mentioned in the results? I missed it.

Commented [KAH5]: What is DTF 14?

Commented [KAH6]: This means we missed 22 DASH at baseline?

Commented [KAH7]: Is this relevant to include? I did not see it as one of the factors. Plus, it is only 2 participants of 126. I vote for removing it as it is such a small number of participants and I did not see it mentioned as one of the factors previously with sex, age, and surgery. We could discuss classifications of the injury types if you think it worthy. There are a couple of different ways to consider injury that have some overlap – fractures, fracture dislocations, and dislocations OR use distal humerus fracture, proximal forearm fracture, dislocation as first approximations. There are more granular aspects of the fracture classifications and elbow dislocation classifications. First question – could injury be a factor? I'd say possibly. Then the next step would be to categorize the injury – we would need to chat about this step.

Commented [KAH8]: This is not a baseline characteristic in Table 1. Is it worthwhile to put the basline DASH in the table? There is no baseline ROM.

sex-related DIF, namely: "*Open a tight or new jar*" (item 1), "*Carry a heavy object (over 10lbs/5kgs)*" (item 11), and "*Put on a jumper*" (item 15) with DIF effects ranging from 4.89% to 5.53% (Figure 1).

For age-related DIF, Monte carlo simulations revealed the optimal threshold for non-negligible DIF is R^2 = 2.7%. Using Glen and Zumbo's recommendation [29], age-related DIF was observed on "*Push open a heavy door*" and "*Wash your back*" (Figure 2). Similarly, surgery-related DIF was observed on two items, namely: "*Manage transport needs (getting from one place to another)*" and "*Tingling (pins and needles) in your arm, shoulder, or hand*" with moderate DIF effects ranging from 5.6% and 6.7 (Figure 3). Further analysis of *Quick* DASH revealed that "*Open a tight jar*", "*Wash your back*", and "*Tingling (pins and needles) in your arm, shoulder or hand*", exhibit moderate sex-, age-, and surgery-related DIF effects, respectively (See Figures 1-3).

The impact of DIF on the estimated DASH functional disability construct across sex, age, and surgery subgroups (Figure 4). Adjusting for sex-related DIF revealed that the adjusted median DASH scores for females were slightly lower scores than initially estimated, while the median DIF-adjusted DASH scores for male patients was slightly higher than initially estimated. However, there were negligible differences in male and female patients' endorsement of functional disability after adjusting for the presence of DIF on these items. Moreover, adjusting for age-related DIF effects resulted in slightly higher DASH scores for both younger and older patients than initially estimated and consequently slightly higher difference in overall DASH between both groups. Finally, adjusting for surgery-related DIF resulted in slightly higher DASH scores for patients who had surgery and lower scores for patients who did not have surgery. Similar impact of DIF was noted on the QuickDASH across age, sex, and surgical subgroups (See Figure A4).

Deleted: Figures 4 describes the

Deleted: effects

Commented [KAH9]: This labelling convention does not match with what is displayed in Figure 4. Please standardize

Commented [KAH10]: I'm having a few challenges with this paragraph. First, it seems like it is more discussion, and less on actual results. I thought about putting it with the last sentence of the 2nd paragraph of the discussion as this part of the results is what supports that sentence. Second, I wonder if this is where the DTF should be mentioned, is the DTF the result? I also mention that latent score is not defined in the statistics section but it is mentioned in the legend for the x-axis of Figure 4. Should the latent score, and qualification of "small as I mention in the comment on Figure 4 be the focus of the result, and then move an abbreviated version of this paragraph to the last sentence of the second paragraph of the discussion?

4. Discussion

This study investigates the presence of DIF in DASH, a widely-used measure of functional disability in patients with elbow contractures. Our study revealed the presence of moderate to large DIF effects in almost a quarter of the DASH and QuickDASH items across sex, age, and surgical subgroups. The majority of these items related to weight-bearing or stress-related such as "*Open a tight jar*", "*carry a heavy object (over 10lbs/5kgs*", "*Push open a heavy door*", "*Wash your back*", "*Put on a jumper*", or a "*Tingling (such as need or pin) in your arm*" which are prone to differential response patterns in patients with elbow fracture/dislocation.

Our study findings are consistent with the evidence from previous studies highlighting the presence of DIF in several DASH and QuickDASH items in patients with disorders of upper extremity. Hung, Voss, Bounsanga, et al. [18] reported about 12 DASH items exhibited moderate to large gender DIF items in a cohort of elbow fracture patients. Forget, Jerosch-Herold, Shepstone, and Higgins [19] also reported the presence of gender DIF in 2 DASH items in patients with Dupuytren contractures. Braitmayer et al [20] also identified problems with the assumption of unidimensionality in the factorial structure and identified presence of DIF in one DASH item. Although these studies have focused on detection of DASH items with moderate to substantial DIF effects, the overall impact of DIF on conclusions about subgroup differences on DASH scores, after adjusting DIF, have not been explored. **Our study shows that these DIF items had a small or negligible impact on the functional disability construct measured by DASH and QuickDASH across age, sex, and surgical subgroups.**

Our study has some limitations. While our analysis might be adequately powered for detecting DIF effects based on OLR, item-response theory models such as 2-parameter graded response models often

Commented [KAH11]: Number placement

Commented [KAH12]: Did they use gender, or sex as their term? We use sex

Commented [KAH13]: Earlier the reference numbers appear at the end of the sentence. Follow the convention of JBJS

Deleted: DAHS

Formatted: Font: Bold

require larger sample sizes for estimating model parameters. Hence, our conclusions, which are based on a small sample size of less than 150 patients, might be influenced by lack of statistical power to estimate these parameters. Our analysis was based on the assumption of unidimensionality for both DASH and Quick DASH. Violation of this assumption can confound the detection of DIF and subsequent conclusions about the impact of DIF in this sample.

Deleted: detect

In conclusion, the presence of DIF in PROMs can threaten the validity of conventional analysis of PROMs to demonstrate treatment effects and subgroup analyses in RCTs. Failure to adjust for DIF in these items might result in reduced statistical power, invalid subgroup comparisons, and biased treatment estimates. We recommend that trialists and investigators conduct preliminary psychometric analysis (such as DIF analysis) of the PROMs prior to evaluating the treatment effects efficacy and other planned subgroup analyses involving PROMs.

References

1. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29(6): 602–8.

2. Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. Qual Life Res. 2000;9(8):887–900.

3. Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. Contemp Clin Trials. 2009;30(4):289–292.

4. Guidance for Industry: patient-reported outcome measures: use in medical product development to support labelling claims Food and Drug Administration. 2009. [Accessed January 10, 2015]. Available from:https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

5. Bottomley A, Jones D, Classens L. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. Eur J Cancer 2009; 45(3):347-353

6. Food and Drug Administration Value and Use of Patient-Reported Outcomes (PROs) in Assessing Effects of Medical Devices CDRH Strategic Priorities. CDRH Strategic Priorities 2016–2017. 2017. [Accessed February 22, 2018]. Available from:https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM588576.pdf.

7. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A, King MT, the SPIRIT-PRO Group. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO Extension. JAMA 2018; 319(5):483-494.

8. Teresi JA, Fleishman JA. Differential item functioning and health assessment. Qual Life Res. 2007;16(Suppl 1): 33–42.

9. Millsap RE. Statistical Approaches to Measurement Invariance. Routledge; 2011.

10. Zumbo BD, Chan EKH, editors. Validity and Validation in Social, Behavioral, and Health Sciences. Cham: Springer International Publishing; 2014.

11. Fleishman JA, Spector WD, Altman BM. Impact of differential item functioning on age and gender differences in functional disability. J. Gerontol B. Pscyhol Sci Soc Sci 2002; 57(5): S275-S284.

12. Slobogean GP, Noonan VK, O'Brien PJ. The reliability and validity of the Disabilities of Arm, Shoulder, and Hand, EuroQol-5D, Health Utilities Index, and Short Form-6D outcome instruments in patients with proximal humeral fractures. J Shoulder Elbow Surg 2010;19(3): 342–8. pmid:20189839

13. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, Bombardier C. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther 2001;14(2): 128–46

14. SooHoo NF, McDonald AP, Seiler JG 3rd, McGillivary GR. Evaluation of the construct validity of the DASH questionnaire by correlation to the SF-36. J Hand Surg Am 2002;27(3): 537–41.

15. Prodinger B, Hammond A, Tennant A, Prior Y, Tyson S. Revisiting the disabilities of the arm, shoulder and hand (DASH) and QuickDASH in rheumatoid arthritis. BMC Musculoskelet Disord 2019; 20(1): 41.

16. Franchignoni F, Giordano A, Sartorio F, Vercelli S et al. Suggestions for refinement of the Disabilities of the Arm, Shoulder and Hand Outcome Measure (DASH): a factor analysis and Rasch validation study. Arch Phys Med Rehabil. 2010 Sep;91(9):1370-7. doi: 10.1016/ j.apmr.2010.06.022.

17. Lehman LA, Woodbury M, Velozo CA. Examination of the factor structure of the Disabilities of the Arm, Shoulder, and Hand questionnaire. Am J Occup Ther. 2011;65(2):169–178.

18. Hung M, Voss MW, Bounsanga J, Gu Y, Granger EK, Tashijan RZ. Psychometrics of the PROMIS PF CAT and DASH in orthopedic elbow patient population. J. Shoulder Elbow Surg 2018; 27(3): 515-522.

19. Forget NJ, Jerosch-Herold C, Shepstone L, Higgins J. Psychometric evaluation of the Disabilities of the Arm, Shoulder and Hand (DASH) with Dupuytren's contracture: validity evidence using Rasch modeling. BMC musculoskeletal disorders. 2014;15:361.

20. Braitmayer K, Dereskewitz C, Oberhauser C, Rudolf KD, Coenen M. Examination of the applicability of the Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire to Patients with Hand Injuries and Diseases Using Rasch Analysis. Patient 2017; 10(3):367-376.

21. Schneider PS, Mohtadi N, **Sajobi T**, Wang M, Garven A, Hildebrand KA. Randomized, placebo-controlled clinical trial evaluating ketotifen fumarate in reduction of post-traumatic elbow joint contracture. Journal of Hand Surgery 2017; 42(9): S50-S51.

22. Gummesson C, Atroshi I, Ekdahl C. The disabilities of the arm, shoulder and hand (DASH) outcome questionnaire: longitudinal construct validity and measuring self-rated health change after surgery. BMC Musculoskelet Disord 2003;4: 11.

Deleted: e

23. Mahabier KC, Den Hartog D, Theyskens N, Verhofstad MHJ, Van Lieshout EMM, investigators Ht. Reliability, validity, responsiveness, and minimal important change of the DASH and Constant-Murley scores in patients with a humeral shaft fracture. J Shoulder Elbow Surg 2016: in press.

24. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, Bombardier C. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther 2001;14(2): 128–46

25. Gummesson C, Ward MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): validity and reliability based on responses within the full-length DASH. BMC Musculoskelet Disord 2006;7:44.

26. Franchignoni F, Ferriero G, Giordano A, Sartorio F, Vercelli S, Brigatti E. Psychometric properties of QuickDASH - a classical test theory and Rasch analysis study. Man Ther. 2011;16(2):177–82.

27. Iordens GIT, Den Hartog D, Tuinebreijer WE, Eygendaal D, Schep NWL, Verhofstad MHJ, et al. Minimal important change and other measurement properties of the Oxford Elbow Score and the *Quick* Disabilities of the Arm, Shoulder, and Hand in patients with a simple elbow dislocation; validation study alongside the multicenter FuncSiE trial. PLoS ONE 2017; 12(9): e0182557.

28. Choi SW, Gibbons LE, Crane PK. Lordif: An R Package for Detecting Differential Item Functioning Using Iterative Hybrid Ordinal Logistic Regression/Item Response Theory and Monte Carlo Simulations. J Stat Softw. 2011 Mar 1;39(8):1–30.

29. Glen MA, Zumbo BD. Differential item functioning results may change depending on how an item is scored: an illustration with the center for epidemiologic studies depression scale. Educ Pscyhol Meas 2003; 63(1): 65-74.

30. **R** Core Team. **R**: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2013.

Table 1: Descriptive Characteristics of Study Participants by Treatment Received

Baseline Characteristics	Ketotifen ($N_1 = 62$)	Placebo ($N_2 = 63$)
Age (mean, SD)	45.8(11.7)	51.0(17.2)
Sex (n, % Female)	25 (40.3)	34(54.0)
Surgery (n, %Yes)	23(37.1)	27(42.9)
Body Mass Index (mean, SD)	26.9(6.2)	27.4(6.4)
Smoking (n, % Non-smoker)	35(56.45)	35(55.56)
Alcohol Use (n, %Yes)	43(69.35)	38(60.32)
Medical History (n, % Yes)	36(58.96)	32(50.79)
Side of Injury (n, % Right)	25(40.32)	26(41.27)
Handedness (n, % Right)	53(85.48)	57(90.46)
Fracture Type (n, % Open)	46(74.19)	47(74.60)
DASH at 12 weeks (mean, SD)	23.2(30.18)	13.03(22.77)
Range of Motion @ 12 Weeks (mean, SD)	122.2(18.2)	126.3(20.2)

Commented [KAH14]: I wonder about the merit of displaying the baseline characteristics by treatment group. My rationale is that treatment group was not one of the 3 factors explicitly defined to test for DIF. Also, the difference in the percentage of females in the 2 groups catches my eye and makes me wonder why this should be in an RCT, and does it affect the analysis – the difference in the percentage of females in the 2 treatment groups. Is treatment part of the modelling? I think having the baseline characteristics helps define the population. Breaking it down by treatment is potentially irrelevant if it is not a factor in the analysis.

Commented [KAH15]: This adds up to 125, not 126 participants. Do we need to add one more here, or change 126 to 125 in the body of the manuscript?

Deleted: 0

Commented [KAH16]: Related to the injury comment earlier, do we want to include it as a factor? How do we want to classify the injury if it is modelled? If it is not part of the modelling, I still see it as a benefit here to describe the population, and I would suggest breaking it down as fractures, and indicating if distal humerus or proximal forearm fractures, and I would also include the number of dislocations, but not get into the subclassification of the dislocation types.

Commented [KAH17]: These aren't baseline characteristics. As an aside, in the main PERK 1 paper we report that DASH is not statistically different between the 2 groups at 12 weeks. Why the discrepancy?

Commented [KAH18]: These aren't baseline characteristics

Figure 1: Distribution of sex-related DIF-effect sizes in DASH items

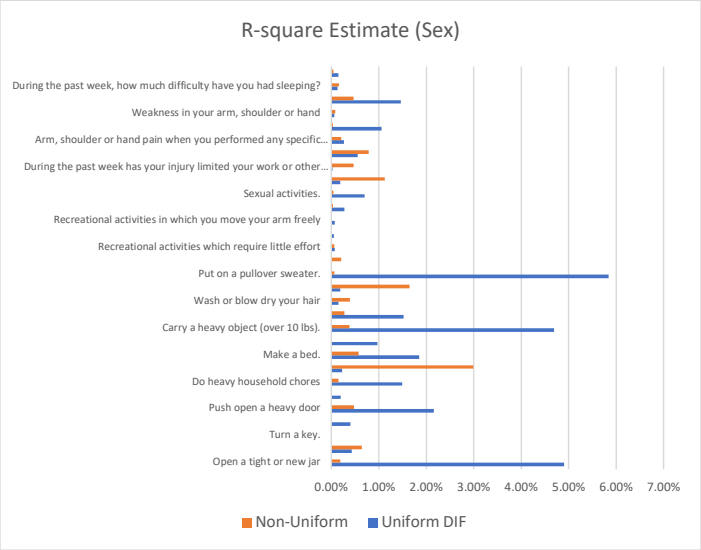


Figure 2: Distribution of age-related DIF-effect sizes in DASH items

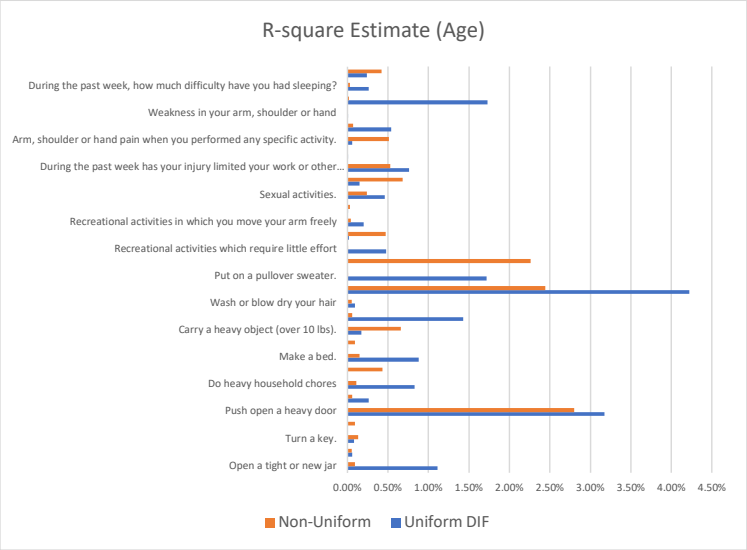


Figure 3: Distribution of surgery-related DIF-effect sizes in DASH items

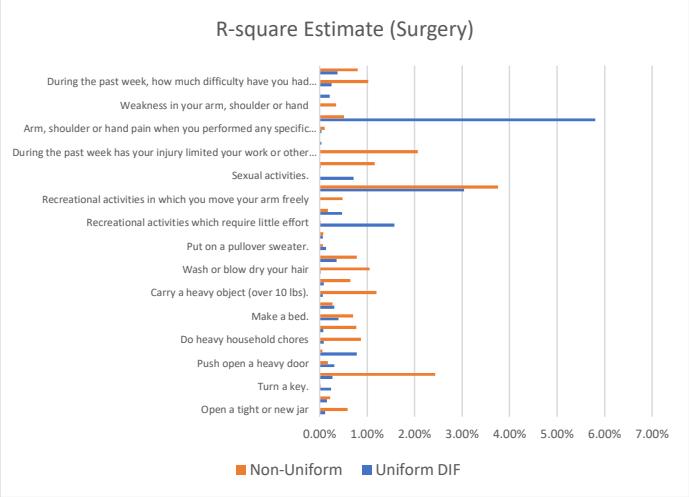
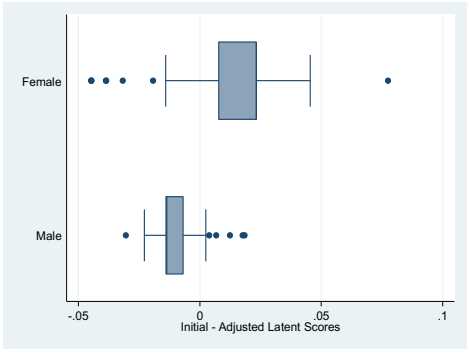
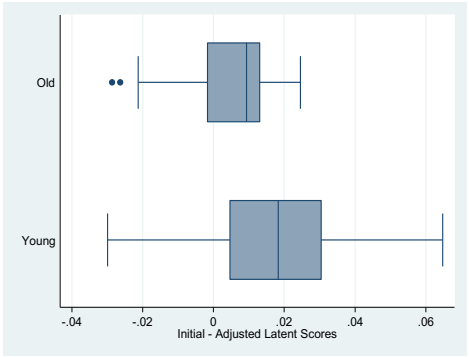
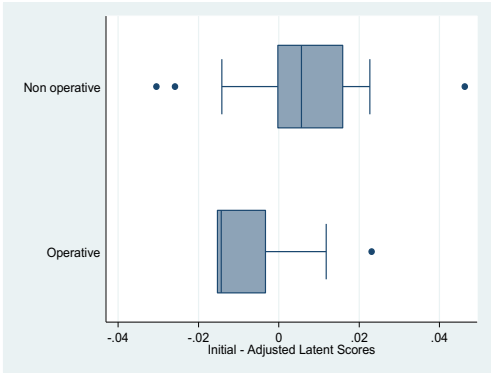


Figure 4: Impact of Sex-, Age-, and Surgery-related DIF Effects on DASH Functional disability







Commented [KAH19]: Is the x-axis a unitless measure? A ratio or some other relationship that ends up with unitless numbers? Is small reflected by the fact that ranges of the latent score are on the scale of 10^{-2}? -.04 to +.04?

Clearly label which is A, B, C and match convention here and in the body of the manuscript.

Appendix

Figure A1: Distribution of age-related DIF effect sizes in QuickDASH items

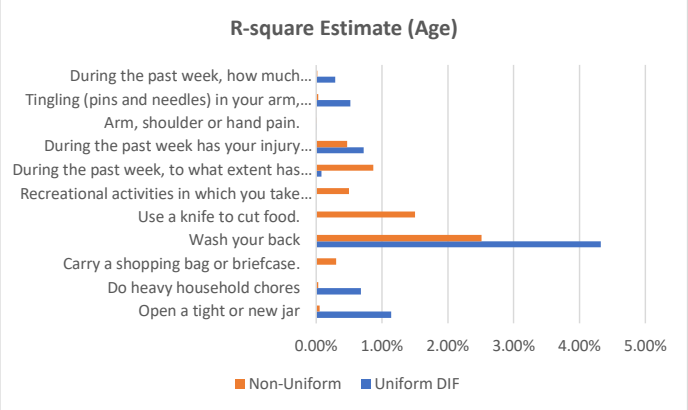


Figure A2: Distribution of sex-related DIF-effect sizes in QuickDASH items

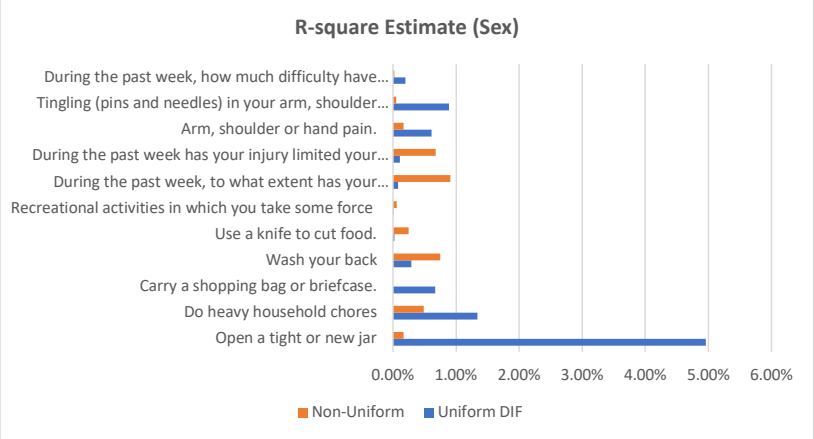


Figure A3: Distribution of surgery-related DIF effect sizes in QuickDASH items

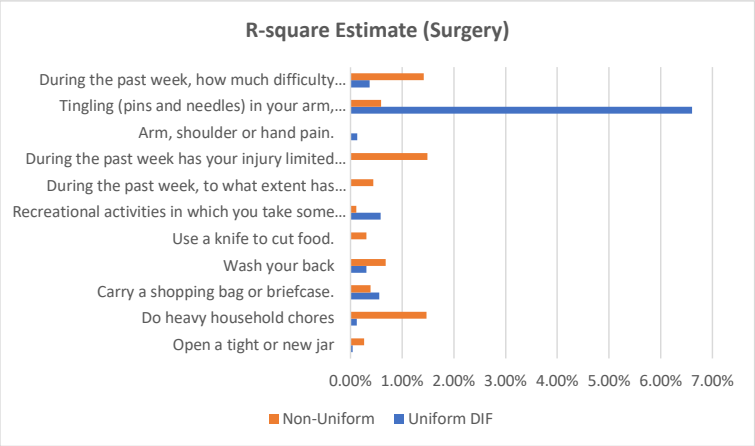
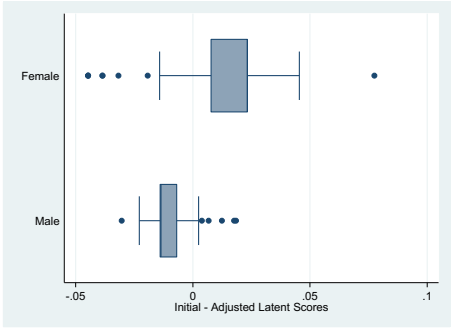
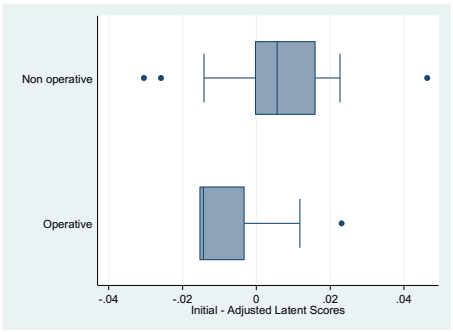
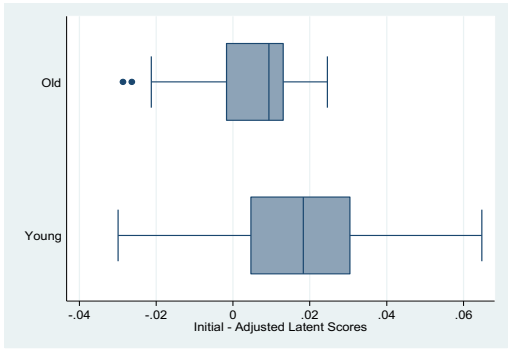


Figure A4: Impact of Age-, Sex-, and Surgery-related DIF Effects on Quick DASH Functional disability







PrEvention of post-traumatic contractuRes with Ketotifen 1 (PERK 1): A pilot randomized controlled trial

Kevin A. Hildebrand MD, FRCSC
Professor, Department of Surgery
Deputy Director, McCaig Institute for Bone and Joint Health
University of Calgary

Prism S. Schneider MD, PhD, FRCSC
Clinical Assistant Professor, University of Calgary
Departments of Surgery and Community Health Sciences
McCaig Institute for Bone and Joint Health

Nicholas G.H. Mohtadi MD, FRCSC
Director and Clinical Professor, Sport Medicine Centre, Faculty of Kinesiology
University of Calgary

Ayoola Ademola MSc
PhD Student, Department of Community Health Sciences
University of Calgary

Neil J. White MD, FRCSC
Clinical Assistant Professor, Department of Surgery
University of Calgary

Alexandra Garven BSc
Research Coordinator, Department of Surgery
University of Calgary

Stephanie Yee BSc
Research Assistant, Department of Surgery
University of Calgary

Richard E.A. Walker MD, FRCPC
Department Head and Professor, Diagnostic Imaging
University of Calgary

Tolulope T. Sajobi PhD
Assistant Professor, Departments of Community Health Sciences & Clinical Neurosciences
University of Calgary

On behalf of the PERK 1 investigators

ABSTRACT

Purpose: Preclinical studies have determined that Ketotifen Fumarate (KF), a mast cell stabilizer and antihistamine oral medication, has promise in the prevention of post-traumatic contractures following fractures or dislocations. A pilot randomized clinical trial (RCT) using a parallel design comparing KF to a lactose-Placebo (LP) group in a 1:1 ratio was conducted at three hospitals in Calgary to assess the feasibility of a future multicentre RCT.

Methods: Adult participants sustaining isolated distal humerus or proximal radius and/or ulna fractures, or elbow dislocations free of arthritis or pre-existing contractures that were within 7 days of injury were eligible to receive either KF 5 mg or LP orally twice daily for 6 weeks. Key objectives were the collection of elbow motion data, use of modalities directed at improving motion, safety, and securing funding and a multicentre network. Randomization was stratified for operative and non-operative management of the injuries in block sizes of four for each site. Participants, care givers and outcome evaluators were blinded to group assignment.

Results: The predetermined sample size of 152 participants was recruited in 37 months. A total of 148 participants were analyzed after withdrawals. Elbow motion measurements during the recovery phase after injury were obtained over the 52 weeks of follow up. The use of modalities to improve motion such as physiotherapy and stretching splints was similar between groups. The adverse events were those expected in an elbow fracture population potentially taking KF and there was no difference between the 2 groups. The

Deleted: +/-

Commented [NJW1]: This is a very long sentence. Consider:

Adult participants sustaining isolated distal humerus or proximal radius and/or ulna fractures, or elbow dislocations identified within 7 days were eligible…

disappearance of fracture lines over time was similar between groups and there was only 1 non-union.

Conclusions: Elbow motion in a fracture recovery population is available for sample size calculations. There were no safety issues detected for this new indication for KF. Funding has been secured and a network of 17 centres across North America identified to conduct a definitive multicentre RCT.

Trial Registration: NCT01902017

Funding: American Foundation for Surgery of the Hand, Canadian Institutes of Health Research, and Workers' Compensation Board of Alberta

Commented [NJW2]: I am surprised you did not present the arc of motion as a primary outcome. Is this because you are writing it up as a pilot. I think it should still find its way into the abstract results.

INTRODUCTION

Injured joints, particularly the elbow, are at risk for permanent loss of motion, or joint contractures that limit the function of an extremity. (1, 2) Limited elbow motion interferes with feeding, dressing, grooming, and reaching for objects, which markedly reduces one's quality of life and function. (3) Many affected individuals are in the 20 – 60 year age group and thus elbow contractures limit productivity. (4) Investigators report operative release of post-traumatic contractures is required in 10-15% of all elbow injuries. (5-8) Canadian population studies report elbow fractures or dislocations at 23,000 events / year nationally. (9-12) Combining the rate of joint contracture and the injury rates gives an estimated >2,500 operative procedures/year for elbow contracture release in Canada.

Commented [NJW3]: Is it useful to add context by mentioning other stiff joints and the burdern associated with them (shoulder, finger joints, etc.)

Laboratory research on post-traumatic joint contractures has implicated a myofibroblast-mast cell-neuropeptide axis of fibrosis in the joint capsule, the critical structure limiting joint motion. (13, 14) Preclinical models of post-traumatic contractures have demonstrated that Ketotifen Fumarate, a mast cell stabilizer that prevents growth factor release, decreased contracture severity by 50% concurrent with decreased numbers of myofibroblasts, mast cells, neuropeptide containing nerve fibres, and measures of fibrosis in the joint capsule, and serum levels of a mast cell specific enzyme, tryptase. (15-17) Ketotifen Fumarate is an oral preparation that has been used in the treatment of chronic asthma for over 40 years in humans. (18, 19) Ketotifen Fumarate is a medication that has anti-anaphylactic properties, due to the prevention of the synthesis and/or release of growth factors and mediators, as well as anti-histamine affects due to H_1 receptor antagonism. (20-22) Reports of overdose as much as 120 times the recommended dose were managed symptomatically with no reports

Commented [NJW4]: Long sentence. Consider breaking into 2 or 3.

Preclinical models of post-traumatic contractures have demonstrated that Ketotifen Fumarate, a mast cell stabilizer that prevents growth factor release, decreased contracture severity by 50%. With this decrease, histopathology revealed decreased numbers of myofibroblasts, mast cells, neuropeptide containing nerve fibres, and measures of fibrosis in the joint capsule. Further, there was a decrease in serum levels tryptase, a mast cell specific enzyme.

of death or ongoing morbidity. (23) Post-market surveillance has confirmed the safety of Ketotifen Fumarate. (18, 19) A search of PubMed and Cochrane Database of Systematic reviews, found no entries associating Ketotifen Fumarate with either non-union (nonunion and non-union) or fracture healing as of November 16, 2018. Search of the Clinical Trials.gov found only this trial (NCT01902017) and the next trial (NCT03582176) as of November 16, 2018.

The overall objective of our research program is to evaluate Ketotifen Fumarate for the prevention of post-traumatic elbow joint contractures following fractures or dislocations. The hypothesis is that Ketotifen Fumarate treatment will significantly decrease the frequency and severity of post-traumatic joint contractures in participants with elbow fractures or dislocations, compared to a lactose-Placebo treatment. In preparation for a future definitive randomized clinical trial (RCT), this pilot trial was conducted to define the variability of outcome measures for sample size calculations, ascertain the potential impact of common modalities on outcome measures, describe the safety and any unexpected adverse effects of Ketotifen Fumarate for this new clinical indication, evaluate the role of injury severity, and establish the methodologies and infrastructure for a future multicenter RCT. The objectives were:

1) Define values for elbow flexion – extension arc of motion in an elbow fracture or dislocation population at 12 weeks post-randomization
2) Determine if unequal use of physiotherapy, stretching braces and non-steroidal anti-inflammatory drugs could affect range of motion (ROM) measures

3) Evaluate the known common side effects of Ketotifen Fumarate of sedation and weight gain for the new indication of post-traumatic contracture prevention
4) Report any unexpected adverse events in an elbow injury population taking Ketotifen Fumarate or lactose-Placebo
5) Observe fracture healing and the development of non-union in an elbow injury population taking Ketotifen Fumarate or lactose-Placebo
6) Explore whether the need for an operation is a surrogate for injury severity
7) Report recruitment rates and the impact of a 7 day recruitment window and isolated injuries
8) Evaluate the choice of an Upper extremity specific and General Health Survey Patient-reported Outcome Measures
9) Obtain grant funding to design and implement the definitive RCT
10) Develop a Multicentre Network to complete the definitive RCT

METHODS

A pilot randomized, blinded trial stratified for injuries requiring an operation or not and hospital with allocation to parallel Ketotifen Fumarate or lactose-Placebo groups in a 1:1 ratio was conducted at three hospitals in Calgary, Alberta, Canada. Pill counts at the 2 week and 6 week follow up visits were instituted with the 25th randomized participant. The thrombocytopenia exclusion criterion was dropped after the 41st randomized participant since it was redundant with the oral hypoglycemic criterion and participants were declining the study because of the blood draw required only for this criterion. Thrombocytopenia has been associated with concurrent Ketotifen Fumarate and oral hypoglycemic use. (24)

Deleted: or not

Participants

The inclusion criteria were participants age ≥ 18 years old with isolated distal humerus (AO/OTA type 13) and/or proximal ulna and/or proximal radius fractures (AO/OTA type 21) and/or elbow dislocations (open fractures with or without nerve injury may be included), injury ≤ 7 days from randomization, ability to give informed consent, and able to comply with protocol and follow-up. Exclusion criteria included pre-existing elbow contracture, elbow arthritis (osteoarthritis, inflammatory arthritis, crystal arthritis or nonspecific monoarticular arthritis), inability to mobilize the elbow within 2 weeks of injury, oral hypoglycemic medications, thrombocytopenia, history of epilepsy, lactose intolerance, non-English speaking, pregnancy, and breast feeding. Pre-existing elbow contractures or arthritis already have loss of motion, while an inability to move the elbow by 2 weeks due to elbow injury instability predisposes to motion loss. A history of epilepsy was chosen because seizures were reported in one overdose case. (23) The safety of Ketotifen Fumarate in human pregnancy has not been established and Ketotifen Fumarate is excreted in Breast milk. (24) Ketotifen Fumarate is not recommended for infants < 6 months of age. (20)

Commented [NJW5]: Do you need a reference?

Fracture classification (Arbeitsgemeinschaft für Osteosynthesefragen [AO] / Orthopaedic Trauma Association [OTA]) and elbow dislocation classification (Desault) were adjudicated by the attending orthopaedic surgeon. (25-28) The Peter Lougheed Centre and South Health Campus receive trauma confined largely to the musculoskeletal system while the Foothills Medical Centre is a level 1 trauma centre. Non-operative participants had all data collected in the fracture clinics while the operative participants had data collected on the hospital inpatient unit and the fracture clinics. Research coordinators gathered baseline data of study

participants including age, sex, smoking history, side injured, hand dominance, and employment status.

Interventions

Participants who signed informed consent were randomized, stratifying for operative / non-operative management and hospital site. Participants received Ketotifen Fumarate 5 mg or a lactose-Placebo immediately after randomization. The medications were administered orally twice daily for a total of 6 weeks post-randomization. All 84 pills were provided to the participants in a bottle at the time of randomization. Ketotifen Fumarate is supplied as 1-mg tablets (Zaditen® DIN 00577308, Ketotifen Fumarate DIN 02230730, TEVA Canada). The central research Pharmacy at Alberta Health Services – Calgary Zone purchased the Ketotifen Fumarate and fabricated and dispensed the treatments to each hospital Pharmacy. Blinding was achieved by over-encapsulation of each treatment with an empty capsule of Capsugel DB® Size AA SW Orange (Capsugel, Morristown, NJ, USA) such that active and lactose-Placebo study medications appeared identical (Figure 1). A No Objection letter was received from the Therapeutic Products Directorate of Health Canada to use Ketotifen Fumarate in joint contractures (File number 9427-D2693-21C, Control number 150110). Participants brought the bottles back at the 2 week and 6 week follow-up visits where the research coordinators counted the remaining pills in the bottle. Any remaining medication at the 6 week follow-up was returned with the bottle to the site Pharmacy for disposal.

Figure 1: Ketotifen and Placebo pill appearance

Operative or non-operative care was not randomized and determined by the participant together with the surgeon based on injury characteristics and treatment goals. An operation could occur before or after randomization, as long as randomization and administration of the first dose happened ≤ 7 days after injury. Analgesia included acetaminophen, opioids and/or non-steroidal anti-inflammatory drugs (NSAID) as required. Mobilization for all participants started within 2 weeks of injury; a home therapy program directed by a physiotherapist consisted of active range of motion exercises for elbow extension-flexion arc and forearm pronation-supination arc performed 3x/day with 20 repetitions. Visits to the physiotherapist every 2 weeks monitored progress and reinforced adherence to home therapy. The index physiotherapy visit to institute the home program and the 6 follow-up visits took up the physiotherapy treatments (maximum 7 visits) as per coverage allowed by Alberta Health Services and standardized the therapy in the two groups until the primary outcome measure at 12 weeks. Participants were allowed to select the location of the physiotherapy visits. Stretching splints were permitted for participants showing a failure to progress more than 10°/month in the extension–flexion motion arc no sooner than 12 weeks post-randomization. The stretching braces could be used for as long as the participant and surgeon decided. Braces stabilizing varus and valgus forces while allowing motion within 2 weeks of injury were approved as required. The recommendation was to use the stabilizing braces to a maximum of 8 weeks postinjury unless in the opinion of the treating surgeon a longer period was necessary to manage instability. The stretching splints and braces for stability included commercially available products or custom fabrications by orthotists at the discretion of the participant and treating surgeon. The use of these interventions were

under the direction of the surgeons within the parameters stated regarding when they could be used and for how long.

Outcomes

Range of motion (ROM) was selected as the outcome measure of interest and on which to base sample size calculations. It is a measure readily obtained in the clinic and participants consistently demonstrate their awareness, and limitations as a result of the lack of motion during their recovery from fractures or dislocations. It is an easy concept for participants to grasp. Range of motion for elbow flexion, extension, flexion – extension arc, and forearm pronation, supination, pronation + supination arc was measured by a research coordinator with a hand held goniometer that had long (25 cm) arms. It has been shown that meaningful changes in flexion or extension are ≥ 5° with this method. (29, 30) Range of Motion was gathered at clinic visits 2, 6, 12, 24 and 52 weeks post-randomization. The elbow flexion – extension arc range of motion (ROM) at 12 weeks post-randomization was chosen as the primary outcome measure on which to perform sample size calculations. This is based on research showing the earliest time that contractures are evident is 12 weeks post injury. (8)

The upper extremity specific Disability Arm, Shoulder and Hand (DASH) and General Health Survey – 12-item Short-Form Version 2 (SF-12v2® Health Survey Standard, Canada [English] © 1992-2002 Medical Outcomes Trust and QualityMetric Incorporated) were used as Patient Reported Outcome Measures. The DASH is a validated tool for disorders of the elbow with a range from 0 (least disability) to 100 (most disability). Ten is the average score in the general population. (31, 32) The SF-12v2® is a norm-based standardized score with mean 50 and standard deviation of 10. (33) The SF-12 has Physical Component Summary (PCS) and

241 Medical Component Summary (PCS) scales. If an individual's score for either scale is <45,
242 health status is below the average range. (34) The DASH and SF-12v2® were completed by
243 the participants.
244
245 A challenge to using ROM as an outcome are the other modalities available to participants
246 that can influence ROM. These modalities include physiotherapy, home therapy, stretching
247 splints and NSAID. (35-37) There is a possibility of non-random differing utilization of
248 standard co-interventions including physiotherapy, stretching splints and NSAID in one of
249 the groups if ROM is not improving with time. The research coordinator asked participants
250 about the use of these modalities at all follow-up visits.
251
252 Weight and sedation were ascertained specifically based on the literature on Ketotifen
253 Fumarate in Cochrane reviews of its use in pediatric asthma and and post-marketing
254 surveillance. (18, 19) Scales on the inpatient units and at the fracture clinics were used by
255 the research coordinator to record the participant's weight. Sedation was recorded in 2 ways
256 – the number of participants reporting it as a symptom to the research coordinator and the
257 number of participants stopping the medication as a result of sedation.
258
259 Adverse events (AE) and serious adverse events (SAE) were gathered from the participants
260 by the research coordinator or the treating surgeon at all follow-up visits. The SAE were
261 reviewed by the trial sponsor. Elbow (re)operations were documented by the research
262 coordinator with the assistance of the treating surgeon. The radiograph evaluation for
263 presence or absence of fracture lines was performed by a musculoskeletal radiologist not

involved with the care of the participants using 12 week follow visit, and if available 24 and 52 week follow-up visit images. Non-union was a clinical diagnosis by treating surgeon based on radiographs and clinical exam.

There were no changes to the trial assessments or measurements. A demonstration version of the SF12 was used by the first 39 participants for a total of 90 scores completed with this version. After July 11, 2014, the correct version, SF-12v2® was completed. The decision to move forward with the definitive RCT would be enacted if the sample size was achieved and data obtained for elbow flex-ext arc ROM, no safety concerns arose using Ketotifen Fumarate in participants with elbow injuries, sufficient funding was secured, and a multicentre network of recruiting sites was identified.

Sample Size

Sample size calculations employed Cohen's standard conventions for a small (f=0.20), medium (f=0.50), and large (f=0.80) effect size in the absence of previously published values on means or variance around the primary outcome measure. (38) An effect size of 0.36 was selected arbitrarily as it was felt to be reasonable, substantive, and clinically relevant. A total sample size of 152 participants was required to detect a difference of ≥36% between the Ketotifen Fumarate and lactose-Placebo groups with 80% power, using a Fixed Effects, 2x2 ANOVA and assuming a (two-sided) α of 0.05. This considered a 10% anticipated dropout rate for patient follow-up throughout the course of the study. (39) The 2x2 ANOVA accounted for the allocation to treatment (Ketotifen Fumarate/lactose-Placebo) but also accommodated the stratification for operative/non-operative management of the injuries.

An interim analysis was performed after the 71st randomized participant completed the 12 week follow-up.

Randomization

A computer-generated, randomization schedule was produced by the trial statistician for each hospital encorporating stratification for operative / non-operative management using blocks of size 4; treatment assignment (i.e., Ketotifen Fumarate or lactose-Placebo) was balanced within each block. Eligible participants were identified by screening of daily fracture rounds and at the fracture clinics at the sites. Treating surgeons or house staff noted those not meeting inclusion or exclusion criteria and this information was given to research coordinators for a screening log with date, participant initials and reason not entered in the study as the only information gathered. Participants who passed the screening stage were asked by the treating surgeon or house staff if they were interested in the trial. Those participants agreeing to learn about the trial were approached by the research coordinator at the fracture clinics, or were approached by the research coordinator or attending surgeon on the inpatient unit depending on the time of potential randomization. After these trial personnel presented the trial and answered questions, interested participants signed informed consent forms. Stratification for operative / non-operative management was determined by the participant and surgeon. Each hospital Pharmacy had a copy of their own randomization schedule that incorporated operative / non-operative management stratification and a pharmacist dispensed the pills according to the randomized allocation. The research coordinator instructed the participant on taking the medication, answered questions, and observed the first dose taken by the participant.

309

310 The participants, research coordinators, treating surgeons, musculoskeletal radiologist, and
311 dispensing pharmacist were blinded to the medication treatment arms of the participants.
312 The active medication and lactose-Placebo appeared identical (Figure 1).

313

314 **Statistical Methods**

315 Descriptive statistics included numbers and percentages of total for discrete variables and
316 mean ± standard deviation ± 95% confidence intervals for continuous variables.
317 Comparisons for discrete variables were completed with a chi square exact test between
318 Ketotifen Fumarate and lactose-Placebo groups while continuous variables were compared
319 with a student t-test between Ketotifen Fumarate and lactose-Placebo groups as well as
320 operative and non-operative groups. Statistical significance was set at $p < 0.05$.

321

322 **RESULTS**

323 Recruitment took place from June 17, 2013 to July 22, 2016. The study started at the Peter
324 Lougheed Centre, the Foothills Medical Centre joined September 11, 2013, and the South
325 Health Campus was added April 1, 2015. Recruitment stopped after the 152nd participant
326 was consented for the study as per sample size calculations. One participant was not
327 randomized after giving consent, resulting in 151 participants randomized. Post-
328 randomization, there were 3 withdrawals, leaving 148 participants. (Figure 2). There were
329 72 and 76 participants in the Ketotifen Fumarate and lactose-Placebo groups, respectively.
330 The Peter Lougheed Centre, Foothills Medical Centre, and the South Health Campus
331 contributed 89, 32, and 27 participants, respectively. The follow-up rates ranged from

146/148 (99%) at 2 weeks to 100/148 (68%) at 52 weeks with similar rates for Ketotifen Fumarate and lactose-Placebo groups. The final participant follow-up was August 3, 2017. A total of 621 participants were screened over the study period of 3 years (Figure 2). The rate of randomizing screened participants was 25%.

The baseline demographic and clinical characteristics of the Ketotifen Fumarate and lactose-Placebo groups were similar (Table 1). The average age was 49 years, the dominant extremity involved in approximately 90% of injuries, and < 10% of the injuries had Worker's Compensation Board claims in both groups. Males represented 58% of the Ketotifen Fumarate group, and and 45% of the lactose-Placebo group. There were 115 fractures, 17 fracture/dislocations and 16 dislocations, split in similar numbers between the two groups. The majority of the fractures were proximal forearm and the dislocations were mostly posterior (Table 1). The average time from injury to starting the medication was 4.5 days in the Ketotifen Fumarate group and 3.8 days in the lactose-Placebo group.

The efficacy outcomes of elbow ROM, DASH and SF12v2® were obtained at all scheduled follow-up visit times. These prospectively gathered data provided information for sample size calculations for the future multicentre trial. There was no statistically significant difference in the 12-week flexion-extension arc ROM or DASH means between the Ketotifen Fumarate and lactose-Placebo groups (Table 2). The SF12v2® scores were not reported as there were 90 forms gathered on a demonstration version of the instrument. When considering the 12-week flexion-extension arc ROM comparing operative and non-operative groups, those having initial operative management had a smaller arc of motion (greater

contracture) of X° ± Y° when compared to the group treated non-operatively A° ± B° (Figure 3). **AYO PLEASE FILL IN X, Y, A AND B**

The frequency of the use of modalities that could affect ROM were not statistically different between the 2 groups at any of the times reported (Table 3). The average number of remaining pills at the 2-week follow-up visit was 60 in the Ketotifen Fumarate group and 58 in the lactose-Placebo group (should be 56 remaining after 2 weeks) while the average number of remaining pills at the 6-week follow-up visit was 9 in the Ketotifen Fumarate group and 7 in the lactose-Placebo group. The percentage of participants reporting they used physiotherapy decreased from about 83-84% at 12 weeks to 10 – 15% at 52 weeks. Home therapy had similar trends when compared to physiotherapy The use of stretching splints was <5% in either group at any of the follow-up time points. Less than a quarter of the participants in either group reported using NSAID at any time point, and there was no obvious decrease over time as there was in physiotherapy and home therapy use.

Safety is considered in terms of AE and SAE (Tables 4 and 5). The a priori designated specific interest AE profiles of sedation, weight change, and radiographic healing showed no significant differences between the 2 groups except for sedation (Table 4). The reported rate of sedation in the Ketotifen Fumarate group (20.5%) was significantly greater than the rate of sedation in the lactose-Placebo group (11.8%). Weight changes at various times were related to baseline measures (Table 4). During the first 6 weeks there was a 3 kg weight loss measured in the Ketotifen Fumarate group and a 1 kg gain in the lactose-Placebo group. Overall in both groups the trend was for weight loss between 1 to 3 kg over the 52 weeks.

Commented [NJW6]: I don't have access to figure 3. You should mention what happens to this difference in ROM over time. Was there still a difference at one year. Was there a difference in DASH scores that would reflect the injury severity as well?

There was no statistically significant difference between the 2 groups for any of the comparisons on weight change. The radiographic appearance adjudicated by the musculoskeletal radiologist revealed no statistically differences between the 2 groups (Table 4). The frequency of those participants in whom the fracture lines were no longer evident increased from 12 to 52 weeks post-randomization.

The rest of the recorded AE occurred at low frequencies between 1 – 8%. These AE are those expected from taking Ketotifen Fumarate or studying an elbow fracture or dislocation population. The AE included dizziness, nausea, loss of appetite, headache, irritability, dry mouth, postoperative pain, stiffness, paresthesia, hematoma, post-operative superficial wound infection treated with antibiotics, limb swelling, medial epicondylitis, olecranon bursitis, suture anchor pull out, implant loosening, implant breaking, and local irritation from internal fixation implants. There was 1 deep venous thrombosis detected after taking medication. With the numbers available, there were no statistically significant differences between the Ketotifen Fumarate and lactose-Placebo groups.

The SAE encountered were discontinuing the study medication or hospitalization for operations after the initial choice of operative or non-operative management of the original elbow injury (Table 5). The number of participants stopping the medication due to an SAE was **2 or 3** in the Ketotifen Fumarate group (dermatitis n=1**,** pulmonary embolus n=1, dizziness n=?) and **0 or 1** in the lactose-Placebo group (dizziness n=?). Unblinding was performed for 1 participant while the trial was active. The number of participants who had an elbow operation or reoperation in the 52 weeks of follow-up was 3 in the Ketotifen

Fumarate group (hardware removal n=1, arthroscopic synovectomy n=1, closed reduction for fracture malalignment n=1) and 4 in the lactose-Placebo group (hardware removal n=3, nonunion n=1). With the numbers available, there were no statistically significant differences between the Ketotifen Fumarate and lactose-Placebo groups. There were no serious unexpected suspected adverse reactions in the study population.

A grant has been obtained from the United States Department of Defense (FY16 PRORP funding cycle eBRAP Log No OR160026). Seventeen centres have been identified through the Canadian Orthopaedic Trauma Society, the Major Extremity Trauma Research Consortium, and the American Society for Sugery of the Hand.

DISCUSSION

Ten objectives concerning outcome measures, safety, participant characteristics and infrastructure were evaluated in this study to assess the feasibility of a future multicentre RCT to assess Ketotifen Fumarate in the prevention of post-traumatic elbow contractures. Other observations from the current trial have informed the upcoming study.

Range of motion is the primary outcome and data has been generated in the healing phase of a fracture population to more accurately advise a sample size calculation. Information about the modalities (physiotherapy, home therapy, stretching splints and NSAID) that could affect the primary outcome, ROM determined that there were no differences between the treatment groups. Adherence to the medication administration was very good as the

remaining pills were on average 2 – 4 more pills than expected at 2 weeks, and 7 – 9 pills unused at the 6 week clinic visit (Table 3). It is also reassuring that the number of pills taken were similar in the 2 groups suggesting no differential effect in this population taking active medication or a lactose-Placebo.

Three objectives considered aspect of safety: evaluating the common side effects of Ketotifen Fumarate – sedation and weight gain; radiographic fracture line absence; other AE or SAE's. Reports of sedation were higher in the Ketotifen Fumarate group (Table 4). The sedation rates were 11 – 21% in both groups, some of this expected in an adult fracture group where analgesics are used. The sedation was most frequent in the first 2 weeks. None of the participants stopped medication because of sedation. Weight loss of 1 – 3 kg was observed in this population of elbow fractures and dislocations. The Cochrane review of pediatric asthmatics noted a 2.1 kg increase in the Ketofien group and 1.6 kg increase in the placebo groups, likely reflecting the growth experienced over the 12 – 32 weeks of the studies reported in the review. (18) There was no statistically significant differences in the number of fracture lines visible when comparing the two treatment groups. The rest of the AE's were infrequent and did not differ significantly between treatment groups. A total of 10 SAE occurred in the study with no statistically significant differences between the treatment groups. The SAE were of 2 types. First, stopping the medication because of SAE. Second, hospitalization for operations related to the elbow injury. There were no suspected unexpected serious adverse reactions. The reported AE and SAE are all expected occurrences in a study population of elbow fractures or dislocations potentially taking Ketotifen Fumarate.

Another objective considered injury severity since conventional wisdom amongst surgeons is that it is a risk factor for developing post-trauamtic elbow joint contractures. An operation was used to define more severe injuries as it is the method to manage fractures where the pieces are markedly displaced, to restore stability to the elbow joint threatened by soft tissue injuries, or to irrigate and debride open fractures. (40) In an analysis of the operative group compared to the non-operative group at 12 weeks post-randomization, the operative group had a significantly smaller flexion-extension arc of motion representing a greater joint contracture. (Figure 3). For the multicentre RCT, the study population will be restricted to operative injuries based on the analysis of the study and respecting the impression of surgeons that more severe injuries are at greater risk for contractures.

Commented [NJW7]: Is your sample size based off of this? Should you mention that in this paper?

Screening, recruitment and the impact of a 7 day cut off was an objective. A total of 621 participants were screened over the study period of 3 years (Figure 2). This represents just over 200 screened cadidates per year. With previous population based studies in Calgary, the elbow injury rate is estimated 400 people / year. (4) Recruitment involved 2 and then later 3 of the 4 adult hospitals in Calgary and none of the 4 area urgent care centres. Thus, screening 200 participants with elbow injuries is a reasonable number. The rate of randomizing screened participants was 25%. A 7 day recruitment window had an impact as this criterion was the second most common reason for not being enrolled in the study (Figure 2). Future recruitment strategies will include communication with surrounding urgent care centres to refer the elbow fractures quickly and streamlining referral centre processes to have these participants assessed as soon as possible.

The decision on the patient reported outcome measures for the multicentre RCT is to keep the DASH and replace the SF12v2. Given that more elbow specific measures such as ROM and the upper extremity survey DASH did not show differences, the general health survey SF12 is unlikely to detect differences. It will be replaced with the Oxford Elbow Score (OES). (31) The OES is a validated elbow specific scale that is responsive to operative interventions. (31, 41)

Commented [NJW8]: Any consideration to PROMISE – I think it is free with your redcap

The last 2 objectives related to infrastructure. A network has been established amongst 17 centres in Canada and the United States. Funding has been secured through the US Department of Defense to support the multicentre RCT.

Despite having study criteria for isolated injuries, there were concurrent injuries in 18 – 22 % in the two groups. This was an unexpected observation. Concurrent injuries occurred at all 3 centres, not just the level 1 trauma centre, highlighting that an isolated injury criterion threatens recruitment. Ten of the 17 centres identified for the multicentre RCT are level 1 trauma centres and the principal investigators at these sites expressed concern for recruitment with an isolated injury criterion. Thus, participants with concurrent injuries will be included as long as they can comply with physiotherapy protocols.

Deleted: Finally, 1 observation of the study population were unexpected. ...

The decision is to proceed to the multicentre Phase II RCT to evaluate dosing and efficacy of Ketotifen Fumarate in the prevention of post-traumatic elbow contractures as all ten

objectives were achieved. Information from this study has led to the incorporation of an elbow-specific score, the Oxford Elbow Score to the SF12v2. Additionally, multiply injured individuals may be included.

Other Information

Pilot Trial Registration Number: ClinicalTrials.gov - NCT01902017. The Pilot RCT protocol is not published. Funding for the study was received through grants from the American Foundation for Surgery of the Hand, the Canadian Institutes of Health Research (Funding Reference Number 123790), and the Workers' Compensation Board of Alberta. The funders had no role in the conduct of the study or the publication of the results of the trial. The pilot RCT was approved by the University of Calgary Conjoint Health Research Ethics Board, original Ethics ID E-24395 and converted to Ethics ID REB 15-0081.

REFERENCES

1. Perry J. Contractures. A historical perspective. Clin Orthop. 1987(219):8-14.
2. Fergusson D, Hutton B, Drodge A. The epidemiology of major joint contractures: a systematic review of the literature. Clin Orthop. 2007;456:22-9.
3. Morrey BF, Askew LJ, Chao EY. A biomechanical study of normal functional elbow motion. J Bone Joint Surg Am. 1981;63(6):872-7.
4. Sheps DM. The incidence of elbow injuries in the City of Calgary. 2006.
5. Doornberg JN, van Duijn PJ, Linzel D, Ring DC, Zurakowski D, Marti RK, et al. Surgical treatment of intra-articular fractures of the distal part of the humerus. Functional outcome after twelve to thirty years. J Bone Joint Surg Am. 2007;89(7):1524-32.
6. Lindenhovius AL, Jupiter JB. The posttraumatic stiff elbow: a review of the literature. J Hand Surg [Am]. 2007;32(10):1605-23.
7. Forthman C, Henket M, Ring DC. Elbow dislocation with intra-articular fracture: the results of operative treatment without repair of the medial collateral ligament. J Hand Surg [Am]. 2007;32(8):1200-9.

8. Myden C, Hildebrand K. Elbow joint contracture after traumatic injury. J Shoulder Elbow Surg. 2011;20(1):39-44.
9. Sheps DM, Kemp KAR, Hildebrand KA. Population-based incidence of proximal radial and ulnar fractures among adults in a Canadian metropolitan area. Current Orthopaedic Practice July/August. 2012;23(4):364-8.
10. Sheps DM, Kemp KAR, Hildebrand KA. Population-based incidence of distal humeral fractures among adults in a Canadian urban center. Current Orthopaedic Practice September/October. 2011;22(5):437-42.
11. Sheps DM, Kemp KAR, Hildebrand KA. Elbow Dislocations in a Canadian Metropolitan Health Region: A 3-Year Population-Based Incidence Study. Shoulder & Elbow. 2010;2(4):281-6.
12. Sheps DM, Reed JG, Hildebrand KA, Hiemstra LA. Supracondylar femur fracture after endoscopic anterior cruciate reconstruction using an EndoButton. Clin J Sport Med. 2006;16(5):428-9.
13. Hildebrand KA, Zhang M, Salo PT, Hart DA. Joint capsule mast cells and neuropeptides are increased within four weeks of injury and remain elevated in chronic stages of posttraumatic contractures. J Orthop Res. 2008;26(10):1313-9.
14. Monument MJ, Hart DA, Salo PT, Befus AD, Hildebrand KA. Neuroinflammatory Mechanisms of Connective Tissue Fibrosis: Targeting Neurogenic and Mast Cell Contributions. Adv Wound Care (New Rochelle). 2015;4(3):137-51.
15. Kopka M, Monument MJ, Befus AD, Zhang M, Hart DA, Salo PT, et al. Serum Mast Cell Tryptase as a Marker of Posttraumatic Joint Contracture in a Rabbit Model. J Orthop Trauma. 2017;31(3):e86-e9.
16. Monument MJ, Hart DA, Befus AD, Salo PT, Zhang M, Hildebrand KA. The mast cell stabilizer ketotifen reduces joint capsule fibrosis in a rabbit model of post-traumatic joint contractures. Inflamm Res. 2012;61(4):285-92.
17. Monument MJ, Hart DA, Befus AD, Salo PT, Zhang M, Hildebrand KA. The mast cell stabilizer ketotifen fumarate lessens contracture severity and myofibroblast hyperplasia: a study of a rabbit model of posttraumatic joint contractures. J Bone Joint Surg Am. 2010;92(6):1468-77.
18. Bassler D, Mitra ADA, Ducharme FM, Forster J, Schwarzer G. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Cochrane Database Syst Rev. 2010(7).
19. Maclay WP, Crowder D, Spiro S, Turner P. Postmarketing surveillance: practical experience with ketotifen. Br Med J (Clin Res Ed). 1984;288(6421):911-4.
20. Grant SM, Goa KL, Fitton A, Sorkin EM. Ketotifen. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma and allergic disorders. Drugs. 1990;40(3):412-48.
21. Craps LP. Immunologic and therapeutic aspects of ketotifen. J Allergy Clin Immunol. 1985;76(2 Pt 2):389-93.
22. Greenwood C. The pharmacology of ketotifen. Chest. 1982;82(1 Suppl):45S-8S.
23. Jeffreys DB, Volans GN. Ketotifen overdose: surveillance of the toxicity of a new drug. British Medical Journal (Clinical research ed). 1981;282(6278):1755-6.
24. Limited TC. Product Monograph Zaditen® (ketotifen fumarate) Tablets 1 mg Syrup 1 mg/5 mL2012:[1-26 pp.]. Available from: http://tevacanada.com/ImageAndPdf.ashx?ObjectId=e7007c3a-32fe-46bb-990c-e55dd3b8826e&DataType=ProductMonographPDF&ObjectMethod=Value&Language=english.

25. Kellam JFMD, Meinberg EGMD, Agel JMAATC, Karam MDMD, Roberts CSMDMBA. Introduction: Fracture and Dislocation Classification Compendium-2018: International Comprehensive Classification of Fractures and Dislocations Committee. Journal of Orthopaedic Trauma January. 2018;32(1):S1-S10.
26. Humerus. Journal of Orthopaedic Trauma January. 2018;32(1):S11-S20.
27. Radius and Ulna. Journal of Orthopaedic Trauma January. 2018;32(1):S21-S32.
28. Desault PJ. A treatise on fractures, luxations, and other affections of the bones: Fry and Kammerer; 1805.
29. Chapleau J, Canet F, Petit Y, Laflamme GY, Rouleau DM. Validity of goniometric elbow measurements: comparative study with a radiographic method. Clin Orthop. 2011;469(11):3134-40.
30. Armstrong AD, MacDermid JC, Chinchalkar S, Stevens RS, King GJ. Reliability of range-of-motion measurement in the elbow and forearm. J Shoulder Elbow Surg. 1998;7(6):573-80.
31. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. Qual Life Res. 2008;17(10):1257-67.
32. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996;29(6):602-8.
33. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.
34. Ware J, Kosinski M, Bjorner J, Turner-Bowker D, Gandek B, Maruish M. User's manual for the SF-36v2 Health Survey. 2nd edn Lincoln. RI: QualityMetric Incorporated2007. p. 81-4.
35. Harvey LA, Katalinic OM, Herbert RD, Moseley AM, Lannin NA, Schurr K. Stretch for the treatment and prevention of contracture: an abridged republication of a Cochrane Systematic Review. J Physiother. 2017;63(2):67-75.
36. Salazar D, Golz A, Israel H, Marra G. Heterotopic ossification of the elbow treated with surgical resection: risk factors, bony ankylosis, and complications. Clin Orthop. 2014;472(7):2269-75.
37. Harding P, Rasekaba T, Smirneos L, Holland AE. Early mobilisation for elbow fractures in adults. Cochrane Database Syst Rev. 2011(6):CD008130.
38. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.
39. Madden K, Scott T, McKay P, Petrisor BA, Jeray KJ, Tanner SL, et al. Predicting and Preventing Loss to Follow-up of Adult Trauma Patients in Randomized Controlled Trials: An Example from the FLOW Trial. J Bone Joint Surg Am. 2017;99(13):1086-92.
40. Schrumpf MA, Lyman S, Do H, Schreiber JJ, Gay DM, Marx R, et al. Incidence of postoperative elbow contracture release in New York State. J Hand Surg [Am]. 2013;38(9):1746-52.e1-3.
41. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, et al. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. J Bone Joint Surg Br. 2008;90(4):466-73.

PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2) – Protocol for a multicenter randomized clinical trial.

Ayoola Ademola[2,3] , Kevin A. Hildebrand[1,2] , Prism S. Schneider[1,2,3], Nicholas G.H. Mohtadi[1,2], Neil J. White[1],Michael J. Bosse[4], Alexandra Garven[1], Richard E.A. Walker[2,5] & Tolulope T. Sajobi[3]

[1]Department of Surgery, University of Calgary, Calgary, Canada

[2]McCaig Institute of Bone and Joint, University of Calgary, Calgary, Canada

[3]Department of Community Health Sciences, University of Calgary, Calgary, Canada

[4]Department of Orthopaedic Surgery, Carolinas Medical Center, Charlotte, USA

[5]Department of Radiology, University of Calgary, Calgary, Canada

Abstract

Background: Injuries and 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 operately treated elbow fractures and/or dislocations.

Methods/design: This study is 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 2U1 and / or 2R1) and/or elbow dislocations (open fractures with or without nerve injury may be included) requiring operative treatment of the elbow fracture or dislocation. 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, patients reported outcome measures at 2, 6, 12, 24 & 52 weeks and impact of KF on safety including serious adverse events, fracture healing and reoperation rates. Descriptive analysis for all outcomes will be reported and analysis of covariance (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 treating post-traumatic joint contractures and improving quality of life after joint injuries.

Trial registration: NCT03582176

Keywords: RCT, Ketotifen Fumarate, contractures, DASH, OES, PCS, ROM.

1. 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 1,200 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 >2,500 operative procedures per year for elbow contracture in Canada (37-41). 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 (6). 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 (7-9). 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 patients with post-traumatic elbow joint

contractures administered within seven 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 reoperation rates.

This is a Phase III randomized, controlled blinded multicentre efficacy trial with three parallel groups and a primary endpoint of elbow flexion-extension range of motion (ROM) arc at 12 weeks post-randomization (Appendix 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 six weeks.

2. 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 2). 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 (Appendix 3). A seven 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 (10). The exclusion criteria are broadly divided in those that predispose to elbow contracture, those that are consequences of using KF or lactose placebo, and those that interfere with the ability follow the protocol (Appendix 3). 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 we used a dose of 5 mg, which is larger than the recommended dose of Ketotifen for the treatment

of chronic asthma (1 - 2 mg twice daily) (6). 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 (11). 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 two and six -week follow-up visits. A relatively short six-week medication administration will facilitate adherence. The only restricted medication that may not be taken simultaneaously with KF is antihistamines. If these are required in the first six 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 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 is obtained with a hand-held goniometer. Loss of ROM is a major reason for patients to consult physicians following elbow injury. One 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) (13-16). 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 (17 - 18). 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 (19 - 22). 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 (23). 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 (Appendix 4). 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 (Appendix 4).

Sample Size

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 (36) 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 30º – 130º flexion-extension arc for activities of daily living (24). Seventeen centres will provide participants for the trial. The 13 sites outside of Calgary are forecasted to enroll 30 particpants each and the 4 Calgary centres are forecast to enroll the remaining 312 participants (Appendix 2).

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) 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. 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 andsex. 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 Biostastician, Project Manager, Orthopaedic Clinical Trialist, and three site Prinicipal Investigators or Project Managers. The TSC will will meet quarterly to review trial performance and adjust the RCT as required based on safety and performance inputs.

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 seven days of injury. Analgesia may be provided by acetaminophen, opioids and/ or NSAID as required. Antihistamines use will be excluded for the six 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 (30-38). 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 six weeks, and a 1-week washout period will be included. Thus, to be considered a SAR, the AE would have to occur within seven 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 six 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 (26 - 34). 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 (35). 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.

3. 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 contracutres is a simpler and safer approach. Contractures

complicate other orthopaedic conditions or procedures, such as total knee arthroplasty and positive results in post-trauamtic contractures could apply to these 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 three 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.

Acknowledgements

Not applicable.

Funding

This grant for this trial was obtained from United States Department of Defense (Funding Reference Number: OR160026).

Availability of data and materials

This is not applicable since the manuscript is a protocol study. Hence no data will be provided.

Authors Contribution

Kevin A. Hildebrand:- Principal Investigator, Fund acquisition, study design, drafting and reviewing of manuscript. Ayoola Ademola:- Draft, revision and submission of manuscript. Prism S. Schneider:- Study design and reviewing of manuscript, Nicholas G.H. Mohtadi:- Review of manuscript, Neil J. White:- Review of manuscript, Michael J. Bosse:- Review of manuscript, Alexandra Garven:- Review of manuscript, Richard E.A. Walker:- Review of manuscript & Tolulope T. Sajobi:- Review of manuscript

Competing interests

There is no completing 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.

Consent to publish

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

Ethical considerations

The ethics approval for the trial was obtained from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary (REB 17-0609). All Protocol modifications will be reported to IRBs/REBs, regulatory bodies and communicated to participating trial sites. 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.

Corresponding Author detail

Ayoola Ademola

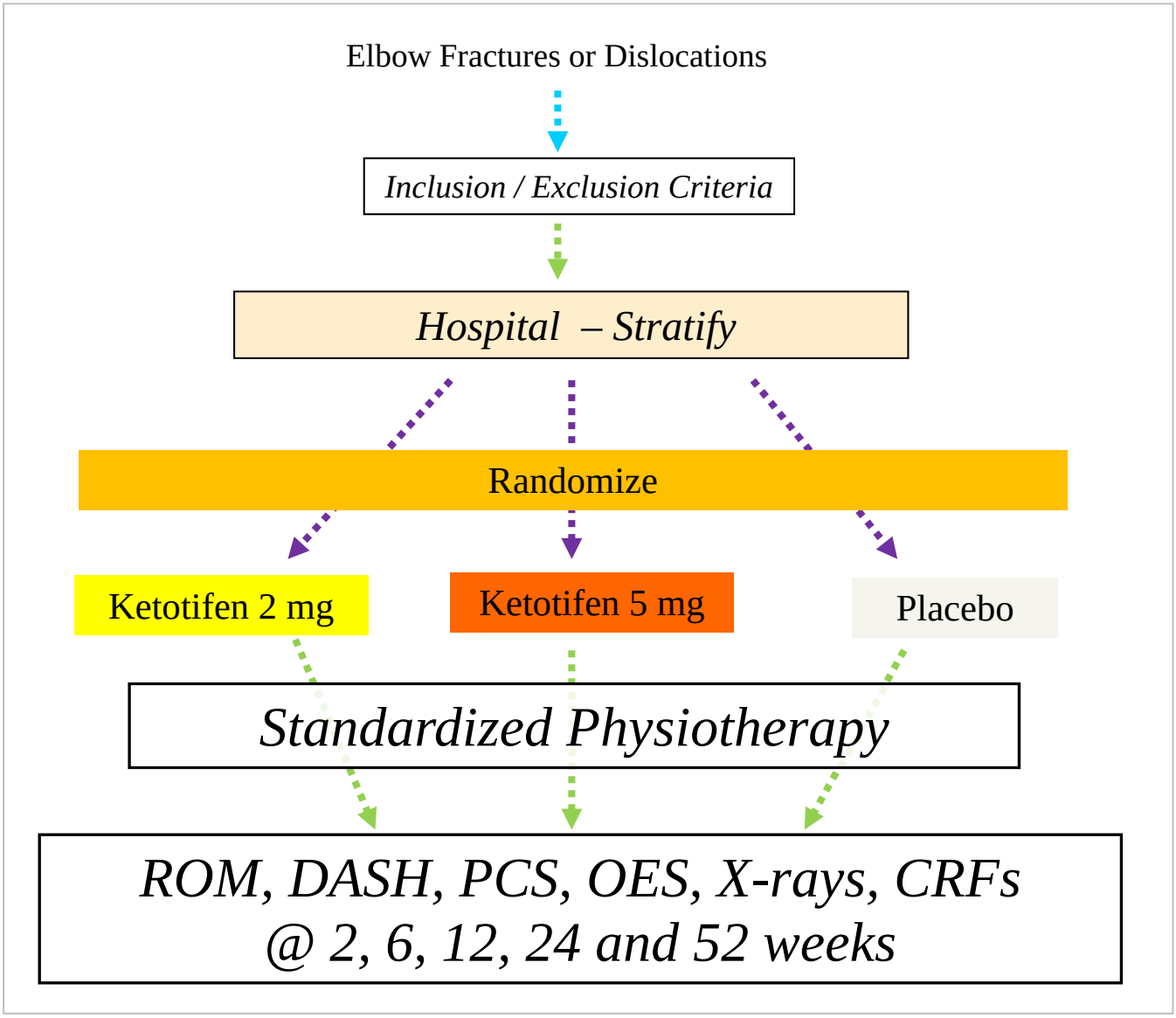
[1]Department of Surgery, University of Calgary, Calgary, Canada.

[2]McCaig Institute of Bone and Joint, University of Calgary, Calgary, Canada.

Email address:– hildebrk@ucalgary.ca

Appendix

1. PERK 2 Trial Design



2. Trial Sites

Peter Lougheed Centre, Calgary, AB
3500 26 Avenue NE
Calgary, AB T1Y 6J4
Canada
403-943-5556

Foothills Medical Centre, Calgary, AB
1403 29 Street NW
Calgary, AB T2N 2T9
Canada
403-944-2932

South Health Campus, Calgary, AB
4448 Front Street SE
Calgary, AB T3M 1M4
Canada
403-956-3687

Rockyview General Hospital, Calgary, AB
7007 14 Street SW
Calgary, AB T2V 1P9
Canada
403-536-3725

Sturgeon Community Hospital, St. Albert, AB
201 Boudreau Road
St. Albert, AB T8N 6C4
Canada
780-492-2398

University of Vermont Medical Centre, Burlington, VT
111 Colchester Avenue
Burlington, VT 05401
USA
802-656-8396

Carolinas Medical Centre, Charlotte, NC
1000 Blythe Boulevard
Charlotte, NC 28203-5812
USA
704-355-6969

McGill University Health Centre, Montreal, QC
Montreal General Hospital
1650 Cedar Avenue
Montreal, QC H3G 1A4
Canada
514-934-1934 ext. 43386

St. Joseph's Hospital, London, ON
339 Windermere Road
London, ON N64 5A5
Canada
519-646-6100 ext. 64640

St. Michael's Hospital, Toronto, ON
30 Bond Street
Toronto, ON M5B 1W8
Canada
416-864-6060 ext. 2608

Sunnybrook Health Sciences Centre, Toronto, ON
2075 Bayview Avenue
Toronto, ON M4N 3M5
Canada
416-505-7686

University of Maryland Medical Centre, Baltimore, MD
22 S Greene Street
Baltimore, MD 21201
USA
704-355-6969

The Ottawa Hospital - Civic Campus, Ottawa, ON
1053 Carling Avenue
Ottawa, ON K1Y 4E9
Canada
613-737-8899 ext. 19217

The Ottawa Hospital – General Campus, Ottawa, ON
501 Smyth Road
Ottawa, ON K1H 8L6
Canada
613-737-8785 ext. 79839

QEII Health Science Centre, Halifax, NS

1799 Robie Street
Halifax, NS B3H 3G1
Canada
902-473-3161

St. Paul's Hospital, Vancouver, BC
1081 Burrard Street
Vancouver, BC V6Z 1Y6
Canada
604-682-2344 ext. 66550

Royal Columbian Hospital, New Westminster, BC
330 East Columbia Street
New Westminster, BC V3L 3W7
Canada
604-520-4855

3. Eligibility Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA

• Adults (**≥ 18 years** or older); skeletally mature
• Injury to the elbow with any of the following:
  o Distal 1/3 humerus fracture (AO/OTA Type 13)
  o Proximal 1/3 ulna fracture (AO/OTA Type 2U1)
  o Proximal 1/3 radius fracture (AO/OTA Type 2R1)
  o Elbow dislocation
• Open fractures with/without nerve injury ***can*** 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
	• **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
	• Oral hypoglycemic medications
	• History of **epilepsy**
	• **Lactose intolerance**
	• **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
	• Any female who is **pregnant or nursing**
	• Severe hepatic impairment
	• Severe renal impairment
	• Total Elbow for fracture treatment
	• Prior Elbow injury or surgery
	• Male or female of reproductive age unwilling to use 2 methods of contraception

	• Concomitant musculoskeletal or visceral injuries preventing elbow physiotherapy • Unwilling or Unable to provide written informed consent • Bilateral elbow fractures and / or dislocations

4. 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

5. Roles, Responsibility and funding

Principal Investigator Dr. Kevin Hildebrand, MD FRCSC

& Sponsor: Health Research Innovation Centre

Co-Investigators: Dr. Michael J. Bosse
Sponsor's Medical Expert
Chief of Orthopaedic Trauma and Director of Clinical Research, CMC
Clinical Chair, METRC
Charlotte, NC

Dr. Nicholas G.H. Mohtadi
Clinical Trialist
Director, University of Calgary Sports Medicine Centre

Dr. Prism S. Schneider
Deputy Principal Investigator
Clinical Assistant Professor, Cumming School of Medicine
Department of Surgery, Department of Community Health Sciences
McCaig Tower, 3134 Hospital Drive NW
University of Calgary

Dr. Richard E. A. Walker
Radiologist
Clinical Department Head, Calgary Zone

Dr. Tolulope T. Sajobi
Biostatistician
Associate Professor of Biostatistics, Cumming School of Medicine
Department of Community Health Sciences
University of Calgary

Funding: United States of America Department of Defense

Research Coordinator: Alexandra Garven

Coordinating Centre: Peter Lougheed Centre
3500 - 26 Avenue NE
Calgary, AB T1Y 6J4

References

1. Fergusson D, Hutton B, and Drodge A. The Epidemiology of Major Joint Contractures: A Systematic Review of the Literature. Clinical Orthopaedics and Related Research. 2007;456:22-29. from: http://dx.doi.org/10.1007/s00198-005-0011-z
2. Sheps DM, Kemp KA, and Hildebrand KA. Population-based incidence of proximal radial and ulnar fractures among adults in a Canadian metropolitan area. Current Orthopaedic Practice. 2012;23(4):364-368.
3. Sheps DM, Kemp KAR, and Hildebrand KA. Population-based incidence of distal humerus fractures among adults in a Canadian urban center. Current Orthopaedic Practice. 2011;22(5):437-442.
4. Sheps DM, Kemp KAR, and Hildebrand KA. Elbow dislocations in a Canadian metropolitan health region: a 3-year population-based incidence study. Shoulder & Elbow. 2010;2:281-286. from:http://dx.doi.org/10.1111/j.1758-5740.2010.00084.x
5. Sheps DM. The incidence of elbow injuries in the city of Calgary [[Internet]]. The incidence of elbow injuries in the city of Calgary. University of Calgary; 2006. from: https://dspace.ucalgary.ca/bitstream/1880/44849/1/Sheps_MSc_2006_Med.pdf
6. Monument MJ, Hart DA, Salo PT, Befus AD, and Hildebrand KA. Neuroinflammatory Mechanisms of Connective Tissue Fibrosis: Targeting Neurogenic and Mast Cell Contributions. Adv Wound Care. 2015;4(3):137-151.
7. Monument MJ, Hart DA, Befus AD, Salo PT, Zhang M, and Hildebrand KA. The mast cell stabilizer ketotifen reduces joint capsule fibrosis in a rabbit model of post-traumatic joint contractures. Inflammation Research. 2012;61:285-92.
8. Monument MJ, Hart DA, Befus AD, Salo PT, Zhang M, and Hildebrand KA. The mast cell stabilizer ketotifen fumarate lessens contracture severity and myofibroblast hyperplasia: a study of a rabbit model of posttraumatic joint contractures. The Journal of Bone and Joint Surgery. 2010;92A:1468-1477.
9. Schneider PS, Johal H, Zhang M, Hart D, Befus A, Salo P, Fan CY, Liang X, and

Hildebrand K. The dose response effect of ketotifen fumarate on post-traumatic joint contractures. Transactions of the orthopaedic research society. 2016. p. 0221.

10. Gallant-Behm CL, Reno C, Tsao H, Hart DA. Genetic Involvement in Skin Wound Healing and Scarring in Domestic Pigs: Assessment of Molecular Expression Patterns in (Yorkshire × Red Duroc) × Yorkshire Backcross Animals. Journal of Investigative Dermatology Volume 127, Issue 1, January 2007, Pages 233-244.

11. Maclay WP, Crowder D, Spiro S, and Turner P. Postmarketing surveillance: practical experience with ketotifen. Br Med J (Clin Res Ed). 1984;288(6421):911-4.

12. Myden C, and Hildebrand K. Elbow joint contracture after traumatic injury. Journal of Shoulder and Elbow Surgery. 2011;20:39-44.

13. Sullivan MJ. PCS The Pain Catastrophizing Scale User Manual 2009. PCS The Pain Catastrophizing Scale User Manual 2009. Montreal; 2009. http://sullivan-painresearch.mcgill.ca/pdf/pcs/PCSManual_English.pdf

14. Finger Stiffness After Distal Radius Fracture Surgery. J Orthop Trauma. United States; 2015;29(10):e414-20.

15. Vranceanu AM, Bachoura A, Weening A, Vrahas M, Smith RM, and Ring D. Psychological factors predict disability and pain intensity after skeletal trauma. J Bone Joint Surg Am. United States; 2014;96(3):e20.

16. Golkari S, Teunis T, Ring D, and Vranceanu AM. Changes in Depression, Health Anxiety, and Pain Catastrophizing Between Enrollment and 1 Month After a Radius Fracture. Psychosomatics. England; 2015;56(6):652-7.

17. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, Jenkinson C, and Carr AJ. The development and validation of a patient-reported questionnaire to assess outcomes of elbow surgery. J Bone Joint Surg Br. England; 2008;90(4):466-73.

18. De Haan J, Goei H, Schep NW, Tuinebreijer WE, Patka P, and den Hartog D. The reliability, validity and responsiveness of the Dutch version of the Oxford elbow score. J Orthop Surg Res. England; 2011;6:39.

19. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, and Carr A. Comparative responsiveness and minimal change for the Oxford Elbow Score following surgery. Qual Life Res. Netherlands; 2008;17(10):1257-67.

20. Iordens GIT, Van Lieshout EMM, Schep NWL, de Haan J, Tuinebreijer WE, Eygendaal D, Van Beeck E, Patka P, Verhofstad MH, Den Hartog D, and FuncSiE Trial Investigators. Early mobilisation versus plaster immobilisation of simple elbow dislocations: results of the FuncSiE multicentre randomised clinical trial. British Journal of Sports Medicine. 2015; doi 10.1136/bjsports-2015-094704.

21. Aitken SA, Jenkins PJ, and Rymaszewski L. Revisiting the 'bag of bones'. Bone Joint J. 2015;97-B(8):1132-1138.

22. Fawi H, Lewis J, Rao P, Parfitt D, Mohanty K, and Ghandour A. Distal third humeri fractures treated using the Synthes™ 3.5-mm extra-articular distal humeral locking compression plate: clinical, radiographic and patient outcome scores. Shoulder Elbow. 2015;7(2):104-9.

23. Dawson J, Doll H, Boller I, Fitzpatrick R, Little C, Rees J, and Carr A. Specificity and responsiveness of patient-reported and clinician-rated outcome measures in the context of elbow surgery, comparing patients with and without rheumatoid arthritis. Orthop Traumatol Surg Res. 2012;98(6):652-8.

24. Morrey BF, Askew LJ, and Chao EY. A biomechanical study of normal functional elbow motion. The Journal of Bone and Joint Surgery. 1981;63A(6):872-877.

25. Rubin DB. Multiple imputation for nonresponse in surveys. Multiple imputation for nonresponse in surveys. John Wiley & Sons; 2004.

26. ICH-E2A. (1995). Guideline for Industry. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

27. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. E6(R1). (1996).

28. ICH-E6. (1996). Guidance for Industry. Good Clinical Practice: Consolidated Guidance.

U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER).

29. Canadian Association of Research Ethics Boards. (2010). Guidance on Reporting of Unexpected Problems including Adverse Events to Research Ethics Boards in Canada.

30. Grahnén A, Lönnebo A, Beck O, Eckernäs S-Å, Dahlström B, and Lindström B. Pharmacokinetics of ketotifen after oral administration to healthy male subjects. Biopharm Drug Dispos. 1992 May;13(4):255-62.

31. Food and Drug Administration Center for Drug Evaluation and Research (2018). Guidance for Industry: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (draft).

32. Food and Drug Administration Center for Drug Evaluation and Research (2009). Guidance for Clinical Investigators, Sponsors, and IRBs: AE Reporting to IRBs – Improving Human Subject Protection.

33. Food and Drug Administration Center for Drug Evaluation and Research (2013). Guidance for Industry and Investigators: Safety Reporting Requirements for IND, BA/BE Studies.

34. Food and Drug Administration Center for Drug Evaluation and Research (2015). Guidance for Industry: Safety Assessment for IND Safety Reporting (draft).

35. Teva Canada Limited. (2012). Product Monograph. Zaditen (Ketotifen Fumarate). http://tevacanada.com/ImageAndPdf.ashx?ObjectId=e7007c3a-32fe-46bb-990c-e55dd3b8826e&DataType=ProductMonographPDF&ObjectMethod=Value&Language= English

36. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, and Bombardier C. Measuring the whole or the parts? Validity, reliability and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. Journal of Hand Therapy. 2001;14:128-146. from:

http://www.ejbjs.org/cgi/content/abstract/84/12/2168

37. 14. Doornberg JN, van Duijn PJ, Linzel D, Ring DC, Zurakowski D, Marti RK, and Kloen P. Surgical treatment of intra-articular fractures of the distal part of the humerus. Functional outcome after twelve to thirty years. The Journal of Bone and Joint Surgery. 2007;89A:1524-1532.
38. 15. Forthman C, Henket M, and Ring DC. Elbow dislocation with intra-articular fracture: the results of operative treatment without repair of the medial collateral ligament. The Journal of Hand Surgery. 2007;32A:1200-1209.
39. 16. Lindenhovius ALC, and Jupiter JB. The Posttraumatic Stiff Elbow: A Review of the Literature. The Journal of Hand Surgery [[Internet]]. 2007;32A(10):1605-1623. from: http://www.sciencedirect.com/science/article/B6WJK-4RB1666-V/2/be065cb2eef3d780d3b3a2680ffb5828
40. 17. Cooney III WP, and Morrey BF. Contractures of the elbow. In The Elbow and its Disorders [[Internet]]. Philadelphia: W.B. Saunders Company; 1993. p. 464-475. from: http://www.sciencedirect.com/science/article/B6WB8-45WHRYN-3/2/361dbdbb1f64f9a48eb2e1857a5f4d99
41. 18. Myden C, and Hildebrand K. Elbow joint contracture after traumatic injury. Journal of Shoulder and Elbow Surgery. 2011;20:39-44.

COTS Meeting Minutes

Wednesday June 19, 2018 1-5pm
Montreal, Quebec
Palais des Congres de Montreal room 518A

Attendees: Mary Amedeo, Richard Buckley, Chad Coles, Zafeiria Glaris, Pierre Guy, Nicole Harris, Kevin Hildebrand, Herman Johal, Amir Khoshbin, Hans Kreder, Jean Lamontagne, Kelly Lefaivre, Ross Leighton, Allan Liew, Shelley MacDonald, Melanie MacNevin, Travis Marion, Paula McKay, Aaron Nauth, Steve Papp, Rudy Reindl, Tina Samuel, Prism Schneider, Leah Schultz, Nigar Sultana, Christina Tieszer, Kelly Trask, Andrew Trenholm, Lynn Vicente, Neil White, Bryn Zomar, Mauri Zomar, Jesse Wolfstadt, Geoff Wilkin, Adrienne Barrie, Stephanie MacBean, Christine Schemitsch, Luana Melo, Sarah Reitzel, Taylor Stranaghan, Martina Vergouwin, Lucy Yang, Chris Graham, Ravi Tuazon, David Wiltshire, Chris Hamilton, Kurt Droll, David Cinats, Jeremy Kubik, Stephen Hunt, Maria Beketskaia, Jodi Gallant, Farhad Moola, Louis LeBlond, Rabail Siddiqui, Shar Seddigh

St. Mike's Update- Aaron Nauth

Flail Chest Study

Complete

- Submitted to OTA – Accepted as highlight paper at OTA
- Submitting to AAOS 2019, COA 2020
- Please finish data collection, resolve queries
- Last recruited patient due for 12 month follow-up in sept 2019
- Targeting high impact journal for manuscript

RIA vs. AICBG Study

- N = 81/104
- 9 active sites
- Established non unions OR bone defects, requiring graft
- Can include patients where bone transport done & will be adding a bone graft upon definitive fixation

Contact **Lynn Vicente: vicentem@smh.ca** for more information

Vancouver B1 Study

- N = 32/104
    - 17 active sites
    - Enrolling for 4 years
    - Most end up being B2's
- Discussion on change of study → is there a lack of equipoise now? Should we re-evaluate & do a prospective cohort?
- Will discuss with co-investigators
- Only 4 in audience would use strut outside of study
- Aaron to look at screening logs to see if it would help to change to prospective → most feel it's not a randomization issue, it's not seeing them
    - Changing to cohort only helpful if patients are being missed from refusal to randomize rather than not being seen
- Is there still a need for struts with the new long plates that don't need the same rotational supports for the struts? (plate up around the trochanter, bicortical screws - Can we add this group as observation group, not randomized?)

- Can use the "new long plates" if that is the plate of choice under the current protocol

Contact **Lynn Vicente: vicentem@smh.ca** for more information

Periprosthetic Distal Femur Fractures Study

- N = 47/94
  - 21 active sites
- Rare fracture, hoping for 2-3 patients per site per year

Contact **Lynn Vicente: vicentem@smh.ca** for more information

A Prospective Randomized Trial of Nonoperative vs Operative Management of Patella Fractures in the Elderly

- N=84
- Primary outcome: KOOS at one year
- Secondary: complication rates, ROM, extensor lag, extensor strength, economic analysis
- Clinical frailty scale → level 3-6
- 3 active sites
- 9 more submitting to ethics/contracts
- Need to be able to do single leg raise with < 30 degrees extension leg

Contact **Lynn Vicente: vicentem@smh.ca** for more information

McMaster Update- Herman Johal

Drivsafe

- N=1315
- Presented Saturday, June 22nd at COA
- Manuscript done and being circulated

FLiP-2

- Femoral IM nailing in lateral vs supine position
- Did international survey, systematic review, database review
- 198 surgeons responded to survey
- Pilot RCT planned
  - N = 100 pts
  - 1 year follow-up
  - Primary: recruitment, retention
  - CT bilateral to assess malrotation
  - Cluster randomization, all patients & site are randomized to one arm for a period then changes
    - ie; 2 months traction table then switch so set-up time is not an issue
- Threshold for intervention of malrotation? → pilot will help define
- Using Pilot to determine secondary outcomes to focus on
- Starting within 2 months once REB at lead site approved → interested sites?
- Looking for funding
- Surgeon must have done either technique 3x in the past year
- will circulate protocol to interested sites
- **Contact daniel.axelrod@medportal.ca or johalh3@mcmaster.ca if interested in participating in the pilot study**

Cannabis studies

- CALM → Cannabis for Acute and Long-standing MSK pain (National Survey)

- Posit → Perceptions in Orthopaedic Surgery on using Cannabis In Treating pain (survey)
    - posters up at COA
    - 1100/1200
        - Will be moving forward with an observational study since RCT has too much red tape even post legalization
            - Eventual RCT
- DICE study → Diagnosis of Intoxication with Cannabis and Emergency Trauma Team Activation

Vancouver Update- Kelly Lefaivre

Far Cortical Locking Study

- 5+ years into study
    - After interim analysis new sample size is 155
- N=142/155
- Recruitment has declined → need to finish recruitment in CAN
- Having recruitment "burnout"
- Hopefully 1 more year to complete recruitment
    - Looking for last few patients from COTS group

Calgary Update- Prism Schneider

Ulnar Shaft Study

- N = 78/100
- Funded $750/patient ($1500 for 1st patient)
- Lead site has approval for "patient inconvenience fee" of $200 (gift cards) to be paid on top of per patient amount if REB approval received at any site
    - $25 each visit at baseline, 2 week, 6 week and 6 months
    - $50 each visit for 3 month and 12 month
- Blinded interim analysis encouraged to continue study

COTS-H

- N=17/125
    - 6 active sites, 3 in progress
- Phase 3: Validation
- Young, active hip trauma patients
- Questionnaires to be administered: COTS-H, iHot-33, NAHS, SF-36 at enrollment (pre-injury), 2 weeks, 6 weeks, 3 months, 6 months, 1 year
- $200/patient ($100 at baseline, $100 at 1 year)
- Looking for additional sites
    - Would like to have sites across country for greater validity
- Received CORL award ($20k) and Alberta Surgery Strategic Clinical Network award ($10k)

Contact **Prism Schneider: prism.schneider@gmail.com** for more information

FIRM

- N=14/100
    - 6 active sites, 2 in progress
- Funding from COTS and OTC
    - $400/patient ($300 + $100 patient inconvenience fee)
- Why can't pts be enrolled @ any time before 3 months?

    - Can consent any time before 3 months, but must be able to schedule removal in protocol window
    - Don't want to approach about secondary surgery too close to index surgery
- When can you cross over?
    - Using intent to treat analysis and this is the reason we are following for 2yrs

Contact **Prism Schneider: prism.schneider@gmail.com** if interested in participating

PERKII- Kevin Hildebrand

- N=702
- Multi-dose RCT: 3 arms- 2 mg ketotifen, 5 mg ketotifen, placebo
    - pills are over-encapsulated (blinded)
- Primary outcome ROM at 12 weeks
    - Randomize within 7 days of injury
- Received DOD funding
    - $4000 start-up, $1275/patient ($675 at enrollment, $300 at 12 week, $300 at 1 year)
    - Pharmacy fees will be paid separately from the start-up and per patient fees
    - No money in budget for x-rays
- Will use RedCAP for CRF data entry
    - Expecting replacement for Alex in a month
- Started April 26
    - Screened 19
    - Recruited 0

Contact **Kevin Hildebrand: hildebrk@ucalgary.ca** if interested in participating

Royal Columbian Update

INSURT Study- David Cinats (trauma fellow)

- N=202
    - 162 randomized
    - 143 following
- $875/patient
- Funding total = $252,000
- Reminder: get true lateral and quality AP with guide wire in prior to reaming

Montreal Update

Humeral Shaft Study- Rudy Reindl

- N = 172/180
- Ottawa group recognized for great recruitment!
- Hoping to present next COA
- Lost ½ funding from AO due to slow recruitment
    - Should set more realistic timeline for recruitment

Distal Radius

- Not written up yet
- Hoping to send to JOT or JBJS

MY01

- Still in ethics
    - waiting on Health Canada ITA approval

London Update- Adrienne Borrie

COTS textbook

- Will be published September 2019

Decipher Study

- Prospective cohort of proximal humerus fractures
- N = 21/700
- 6 active sites, 7 in progress
- $1000 start-up fee; $500/patient

Contact **Adrienne Borrie: Adrienne.Borrie@lhsc.on.ca** if interested in participating

Distal Radius Cohort

- N = 20/650
    - ≥18yrs, isolated #
    - Baseline, 1wk, 2wks, 3 wks, 6wks, 3m, 6m, 1yr, 2yr
    - 2yr follow-up
- Only at London currently
- Funding is limited

Contact **Adrienne Borrie: Adrienne.Borrie@lhsc.on.ca** if interested in participating

Pilon Fracture Study

- N = 88
- ORIF vs primary fusion in complex tibial pilon fractures
    - Age ≥60 , C2 or C3 tibial pilon #
    - 2yr follow up
- OTA grant submitted

Biocomposites Stimulan Study

- RCT of infected bony defects and non-unions in tibia
    - standard of care vs. antibiotic impregnated calcium sulfate (Stimulan)
- N = 0/100
- Primary outcome: re-operation
- Approved at LHSC
- Will cover REB application and annual approval
- $1500/patient

Contact **Adrienne Borrie: Adrienne.Borrie@lhsc.on.ca** if interested in participating

Halifax Update- Ross Leighton

Stimulan Study

- N = 30 (complete)
- Accepted at OTA for podium presentation

Proposals

Isolated Ankle Arthrodesis vs Hindfoot Fusion for isolated ankle arthritis – Bashar Alolabi

- Does TTC fusion decrease nonunion or complication vs isolated ankle fusion?
- Is there a difference in physical function/outcome scores?
- Is subtalar fusion necessary?
    - Surgeon preference on part & randomization
- Propose multicenter COTS Trial
    - Isolated ankle fusion vs TTC fusion
    - Open or arthroscopic (surgeon preference)

- 6wks NWB in cast/boot
- 1yr f/u

- Comments:
  - Talk to COFAS → plan to share COTS/COFAS
  - What is sample size? → not formally calculated ~100
  - Allow use of PDGF → some want to use regularly, investigator discretion
  - Control fixation type → too limiting
  - Gait only for sub sample → very costly, not available at every site, sub sample for sites that have gait lab

<u>GATOR RCT: Geriatric Acetabular fracTures: Open reduction internal fixation vs Replacement</u> – Amir Khoshbin

- N = 118 (accounting for 10% LTF)
- Tweaked protocol after COTS survey
- COTS survey:
  - 2/3 of respondents would not randomize all
  - No consensus on # patterns to inclusion/exclusion
  - Poor consensus on patient characteristics to inclusion/exclusion
- Primary outcome: Will THA + ORIF improve pain and function over ORIF alone measured by Oxford Hip over 24 months? → Oxford Hip (3, 6, 9, 12, 24 months)
- 7 sites have shown interest
- Enrollment → question on equipoise → Working Acetabular Group (WAG)
  - Want 3/5 responses to agree there is equipoise (of 13) in order to randomize
  - Suggestions:
    - too complicated → let treating physician decide
      - If equipoise, randomize – if no equipoise, prospective f/u
    - Standardize rehab protocol
    - Standardize weight bearing protocol
    - Leave surgical treatment to discretion of treating surgeon
    - Possible that prospective cohort is the best design for this study (only 1 other to date ~40 patients)
    - Build in a fragility index
    - 118 pts needed for repeated measures oxford → increasing > 400 for single time point
- Consensus:
  - Age 60+
  - Equipoise by center not WAG
  - Prospective cohort possibly leading to a RCT

<u>C3PO Trial (The Canadian Prospective Pragmatic Perilunate outcomes Trial</u> – Neil White

- Wrist evaluation Canada (WeCan) + COTS joint venture
- Rare enough injury to capture all → most referred to tertiary hospital
- Incidence & injury characteristics
- Long term outcomes (5-10yrs)
- RCT for purely ligamentous scaphoid lunate
- Registry of all perilunate #
  - To establish database of accurate incidence & demographic info

    - Recruit cohort concurrently
    - Possible RCT in future
    - N = 80
    - MCID = 10 on DASH
- Poorly funded currently (CORL grant $20,000)
    - Suggest WCB per province

UK Active study: pilon fractures ring fixator vs locked plating – Pierre Guy (Matt Kosta)
- Pilon # → ring fixation vs locked plates
- Essentially no one in COTS uses ring fixation
    - 1 surgeon in Montreal does; has been in contact with Matt Kosta
- Identifying interest

PRECICE nail – Pierre Guy
- Survey of COTS completed
- UBC survey results → feedback/brainstorm
- $20,000 per nail
    - Precise nail not approved at Vancouver General – too expensive
    - Is used at Royal Columbia, Calgary
- Recent paper from single center shows cost effectiveness of this nail
- ~8/14 surgeons have used nail
- Cost is main issue in Canada
- Is there interest for using this type of device for any trial
- JAAS – recent publication → shared impairment in number of operations
- Comment:
    - Pediatrics is biggest user
- Contact **Pierre Guy: pierre.guy@ubc.ca** if interested in pursuing

Phase 3 Bone Healing Accelerant Trial as an adjunct to standard of care in Open Tibia Fractures – Ross Leighton
- Bone Healing Accelerant in open tibia fractures
- Any nail size, screws optimal
- Many interim analysis planned
- Carmell may contact sites for interest
    - not accepting input on protocol

Other Business

Canadian Orthopaedic Foundation – Pierre Guy
- Charitable foundation created by COA
    - Research, Education and Care
    - www.whenithurtstomove.org
- Presenting at each subspecialty society at COA
- Four years ago gave away $35,000; this year $270,000
- Encourage members to apply for grants (COLR Award)
- Looking for volunteers to help with research review process → contact Pierre Guy
    - Want each subspecialty to provide 2 people

- Industry support and public support; Surgeon engagement to donate
- Develop one payer from each sub-specialty with top 3 priorities for research project
- Research Priorities:
    - A.I
    - Virtual Care
    - Innovation (disruptive, high impact)
- Rick Buckley key factors:
    1) Young investigator
    2) Good mentor - Experiences collaborator
    3) Starter project
    4) Prospective
    5) Good budget
    6) Basic science and clinical projects

<u>COTS Grant Competition Award</u>

- Submissions due August 15th

<u>COTS Financial Update</u>

- $5000 from Biocomposites
- ~ $30k from Depuy/ Synthes
- ~ $10k for OTA – international (room for 5 more articles)

<u>COTS Authorship guidelines and Bylaws</u>

- For authorship make COTS main author so everyone can add to their CV
- Membership structure
    - Should we contact those who haven't recently attended?
    - Should a fee be charged? (COFAS charges $50 membership fee)
        - Survey to be sent out to the current membership

Additional Items

COA Trauma Program and CPD Committee – Steve Papp

- Looking for topics for future education sessions
- Ideas:
    - consider small group case discussions or offsite labs (similar to COFAS)
    - possibly create a budget to fund guest speakers

Contact **Steve Papp: srpapp21@gmail.com** with suggestions or to volunteer

Next COTS meeting: **OTA- Denver (September 26, 2019- 7am-12pm)**

Adjourn 4:55pm

COTS Meeting Minutes

Thursday, Sep 26, 2019 7am-noon
Denver, CO
Agate Room, Hyatt Regency Denver

Attendees: Aftab Akbari, Rashed AlQudhaya, Nuno Alves Batista, Phumeena Balusuberamaniam, Henry Broekhuyse, Richard Buckley, Chad Coles, Niloofar Dehghan, Paul Duffy, Nicole Harris, Ed Harvey, Jennifer Hidy, Kevin Hildebrand, Richard Jenkinson, Herman Johal, Denis Joly, Amir Khoshbin, Kelly Lefaivre, Ross Leighton, Mike Lemke, Karin Lienhard, Allan Liew, Melanie MacNevin, Mike McKee, Matt Menon, Diane Nam, Aaron Nauth, Bert Perey, David Sanders, Christine Schemitsch, Emil Schemitsch, Prism Schneider, Taylor Stranaghan, Kelly Trask, Andrew Trenholm, Lynn Vicente, Jeff Yach, Mauri Zomar

STUDY UPDATES

St. Mike's Update

Flail Chest Study (Aaron Nauth**)**

- Congratulations: highlight paper at OTA!
- Keep collecting data for final follow-ups
    - Expect queries on previously submitted data
- Manuscript planned once follow-up is complete

RIA vs. AICBG Study (Aaron Nauth**)**

- N = 85/104
    - Recruited 14 since last OTA
- Need 19 more to finish – push to finish recruitment by next OTA

Vancouver B1 Study (Aaron Nauth**)**

- N = 35/104
    - Recruited 11 since last OTA; 3 since COA
- Reviewed screening logs since COA meeting
    - most exclusions are because they are not Vancouver B1 fractures
    - small number not amenable to both treatments
        - will dig further into exclusions
- Need 69 more patients from 17 sites:
    - If each site contributes 2 patients/year we will be done in 2 years

Periprosthetic Distal Femur Fractures Study (Aaron Nauth**)**

- N = 49/94
    - Recruited 8 since last OTA
- Rare fracture, hoping for 2-3 patients per site per year
- Study coordinators: Please review patient questionnaires for completeness before the patient leaves clinic.

Patella Fracture RCT (Aaron Nauth**)**

- N=84
- 4 active sites; 8 more submitting to ethics/contracts

Contact **Lynn Vicente: milena.vicente@unityhealth.to** for more information

DIFFIR Study (Amir Khoshbin**)**

- Distal Femur Fractures: Fixation vs. Distal Femoral Replacement
- Awarded $80,000 from OTA

- Primary outcome is Oxford Knee
- ~55/group, 2-year follow-up
- Using REDCap
- Includes prospective follow-up for those refusing randomization
- Current inclusion is age 65+ (in line with the hip literature for distal femoral replacement)
    - Concerns raised about randomizing healthy, active 65-year old to replacement
    - Suggested using clinical frailty
- If interested, contact Kelly for protocol: kelly.trask@nshealth.ca

GATOR Study (Amir Khoshbin**)**

- Prospective cohort
- Will update at COTS meeting in June

Upcoming Studies from St. Mike's (Aaron Nauth**)**

- 5-year follow-up of ulnar nerve study patients
    - One-time clinic follow-up and outcome measurements
        - Suggestion from COTS to include EMG
    -
    - $100/patient
    - REB approval at SMH
    - Lynn will contact sites who participated in the original study
- 10-year follow-up of AC Joint study patients
    - One-time clinic follow-up and outcome measurements
    - REB pending at SMH
    - Lynn will contact sites who participated in the original study
- Shoulder Registry (TSA, RTSA and hemi)
    - REB pending at SMH
    - REDCap housed at SMH
    - Starting local (Jeremy Hall), expanding across Ontario and across Canada if interest
    - Contact **Lynn Vicente: milena.vicente@unityhealth.to** if interested

McMaster Update- Herman Johal

FLiP

- Femoral IM nailing in lateral vs supine position
- Pilot RCT planned to assess feasibility
    - N = 100 pts
    - 1 year follow-up
    - CT bilateral to assess malrotation
    - Cluster randomization, all patients & site are randomized to one arm for a period then changes
        - ie; 2 months traction table then switch so set-up time is not an issue
    - Gait analysis (at 1 year) substudy at applicable sites
        - Approached at 6-months for substudy recruitment
- REB at lead site
- Applying for funding
- Will circulate protocol to interested sites

- Suggestions from COTS:
    - Ask surgeon preference if they were not participating – see if it changes after study
    - Should fracture table position be specified in protocol? Scissor position vs. up & away
- **Email if you are interested in the pilot at your center: daniel.axelrod@medportal.ca, scottta@mcmaster.ca, johalh3@mcmaster.ca**

COTS Trials Paper

- Reviewed all COTS studies
- Result: it takes ~ 10 years from COTS proposal to publication
    - ~4.5 years from completion to publication
- Was done as an informal review – going to re-do as a systematic review and may expand to other trauma RCTs
- Comments/suggestions:
    - Number of publications per grant is often more than number of grants from OTA because of secondary publications – need to capture
    - Will help inform grant funders how long it takes to get published so money isn't clawed back
    - Despite successful recruitment/completion of syndesmosis study, Arthrex was unhappy with publication timeline and not interested in funding again
        - Delay was in editorial process with JOT and not in author's control

Vancouver Update- Kelly Lefaivre

Far Cortical Locking Study

- 5+ years into study
    - After interim analysis new sample size is 155
- Need to recruit 14 more patients
- New contact person for study: Irene Leung, irene.leung@vch.ca
- Push to complete recruitment by COA!

Calgary Update- Prism Schneider

Ulnar Shaft Study

- N = 78/100
- Funded $750/patient ($1500 for 1st patient)
- Lead site has approval for "patient inconvenience fee" of $200 (gift cards) to be paid on top of per patient amount if REB approval received at any site
    - $25 each visit at baseline, 2 week, 6 week and 6 months
    - $50 each visit for 3 month and 12 month
- Blinded interim analysis encouraged to continue study
- Should be good opportunity for secondary papers from this

Syndesmosis Study

- Manuscript finally published
- One-year CT data presented at this OTA

COTS-H

- Patient-reported surveys
- N=30/125
- $200/patient ($100 at baseline, $100 at 1 year)

- Looking for additional sites
    - Would like to have sites across country for greater validity

Contact **Prism Schneider: prism.schneider@gmail.com** for more information

FIRM

- Removal vs retention
- N=19/100
- Funding from COTS and OTC (up for review)
    - $400/patient
- Currently consent is at 6 weeks (±2) – amendment planned to change to within 3 months of index procedure

Contact **Prism Schneider: prism.schneider@gmail.com** if interested in participating

PERKII- Kevin Hildebrand

- N= 9/702, screened 98
- Multi-dose RCT: 3 arms- 2 mg ketotifen, 5 mg ketotifen, placebo
    - pills are over-encapsulated (blinded)
- Primary outcome ROM at 12 weeks
    - Randomize within 7 days of injury
- Received DOD funding
    - $4000 start-up, $1275/patient ($675 at enrollment, $300 at 12 week, $300 at 1 year)
    - Pharmacy fees will be paid separately from the start-up and per patient fees
    - No money in budget for x-rays
- Patients can start study meds before surgery
- Contact **Kevin Hildebrand: hildebrk@ucalgary.ca, Taylor Stranaghan taylor.Stranaghan@ahs.ca, or Gerry Duque gerardo.duque@ucalgary.ca** if interested in participating

Royal Columbian Update - Mike Lemke

INSURT Study

- N=179/202
- Medial parapatellar approach is acceptable as suprapatellar
- Reminder: get true lateral and quality AP with guide wire in prior to reaming
- Reminder: have patients do kneeling and standing tests
- Reminder: please try and observe study windows

Montreal Update & Halifax Update – Ross Leighton

Humeral Shaft Study

- N = 174/180
    - Please keep recruiting to finish!

MY01

- Montreal and Halifax waiting on Health Canada ITA approval
    - Expected study start mid-November
- COTS-wide study planned after device is licensed by Health Canada (i.e. not investigational)
    - Expected 2020

London Update - Emil Schemitsch

Decipher Study

- Prospective cohort of proximal humerus fractures
- N = 30/750
- Fully funded for 5 years: Funding: PSI; CIHR; CORL; OTA
    - $1000 start-up fee; $500/patient
- Current protocol v3, 16OCT 2018
- New amendment coming soon pending REB approval
- Still looking for more sites
- Contact **Melanie.Macnevin@lhsc.on.ca** if interested in participating

Distal Radius Cohort

- N = 30/650
- Only at London currently
- Planning change from 3 follow ups to just 1 follow up visit within first four weeks
- Funding is limited ($70/patient from OTA) – applying for grant
- Contact **Melanie.Macnevin@lhsc.on.ca** if interested in participating

Pilon Fracture Study

- N = 88
- ORIF vs primary fusion in complex tibial pilon fractures and severe ankle fracture equivalents
- OTA grant submitted (not funded)
- Inclusions/exclusions have changed and may change again in response to grant comments
- Method of fusion may change based on grant comments
- Discussion:
    - Is this still worth pursuing?
        - Yes, but exclude healthy/ high-energy
        - Don't base inclusion on age – use frailty score
    - Do we have enough fracture population to complete study?
        - Will be a tougher consent discussion

Biocomposites Stimulan Study

- RCT of infected bony defects and non-unions in tibia
    - standard of care vs. antibiotic impregnated calcium sulfate (Stimulan + 1 g Vanco + 240 mg Tobra)
- N = 0/100
- Primary outcome: re-operation
- Approved at LHSC
- Will cover REB application and annual approval and $1500/patient
- Current protocol: V2.1; dated 12 SEP 2019
- Looking for additional sites
- Contact **Melanie.Macnevin@lhsc.on.ca** if interested in participating

Ulnar Nerve Study

- Two-year results being presented at this OTA
- Manuscript in preparation for submission by end of 2019

NEW PROPOSAL

Development and Preliminary Assessment of a Patient-Reported Functional Outcome Measure for Proximal Humerus Fracture Patients (PROM for Proximal Humerus Fracture) – Emil Schemitsch

- Has OTA funding
- Stage 1: Preliminary Questionnaire Development
    - Item Generation: generate an initial item pool using existing outcome measures identified via previously completed systematic reviews
    - Stage 1a - Expert Consultation: 5 PHF experts evaluate the relevancy of items with respect to face and content validity
    - Stage 1b - Preliminary Patient Survey: 50 PHF patients within 1 year of their fracture rate items
    - Stage 1c - Patient Focus Groups: 21 patients to participate in 3 focus groups (7 patients each), assess patient preferences for response options in terms of frequency, bother, difficulty, or extent
- Stage 2: Pilot testing
    - Sample of 10 PHF patients (different from those included in item development and reduction) for this stage
    - Conduct pilot testing to identify any difficulties with administration and assess item clarity
- Stage 3: Preliminary Evaluation of Measurement Properties and Refinement
    - Ssample size of 150 patients within two-weeks of fracture (potential overlap with DECIPHER?)
- Comment: AO group is also looking at PROMS
- Contact **Melanie.Macnevin@lhsc.on.ca** if interested

OTHER BUSINESS

Proposed Manuscript: COTS should write a paper on the challenges of operative vs. non-operative randomized trial that can be presented to funders (ulnar shaft, humeral shaft).

- Apologies – I wrote this down but did not make note of who said it. --KT

Canadian Orthopaedic Foundation – Kevin Hildebrand for Pierre Guy

- Charitable foundation created by COA, separate from COA
- Mission: pain-free mobility for life
- CORL awards – has increased amount of funding: ~$250 k/year
    - Approx. 40 applications each year; 13 funded
    - COTS members have been successful
        - Encouraged to keep applying
- Canadian subspecialty engagement needed:
    a. Want bigger research ideas to approach donors/industry (e.g. innovation, AI, virtual care)
    b. Partner in fundraising; named awards (e.g. CSES award for best paper at COA funded by CSES)
        i. COF can help manage awards
        ii. COTS already uses COF to keep our money
    c. Adjudicating awards (CORL) – looking for reviewers from subspecialties
- COF wants to collaborate with subspecialty societies

- How would COTS like to interact with COF?
- Private donors often give to local but it's a struggle to get them to give to a national group
- COF looking for things they can add to their presentations to donors; more fleshed out ideas so they can approach big donors.

COTS Grant Competition Award

- 4 applications this year
- Awarded to Herman Johal and Daniel Axelrod for The FLiP Study
- Grant review comments will be sent out to applicants
- Discussion: Is this the best use of COTS money or should we be putting it elsewhere? (e.g. have funded supplemental journal issues in the past)
    - Could it be used to help finish off current studies that have lost funding or momentum?
        - Tough to operationalize: competition? Application? Who decides?
        - Is that unethical? (incentive to researchers)
        - Winning a COTS grant looks good for young investigators and helps when seeking additional funding
    - Should we use the funds to finance another meeting (i.e. at AAOS) to energize people between OTA and COA to keep studies recruiting?
    - Should it be put toward funding a committee within COTS that could work to decrease the lag between finishing a study and publishing it?
    - Put forward for future discussion

COTS Bylaws

- Should we charge a membership fee?
    - Good to have info going out to larger group
    - Fee is not a deterrent
    - People signing up but not contributing
    - Should we contact people who have not attended/contributed for 3 years?
- Status quo for now

COA Trauma Program – Ross Leighton for Steve Papp

- ICLs Thurday/Friday: Need 2
    - Niloofar Dehghan and Bert Perey volunteered to be moderators
- Trauma paper session Thursday – need 3 reviewers/moderators
- Combined symposium with pediatrics
    - Suggested to have it more adolescent than toddler
- Need one main trauma symposium
    - Suggested geriatric fracture session – focus on how to achieve immediate/early weight bearing for all body parts (acetabular fractures, ankle, peri-prosthetic, etc.)
        - Ross Leighton and Amir Khoshbin have volunteered
- Sawbones workshop?
- Contact **Steve Papp: srpapp21@gmail.com** with suggestions or to volunteer

Next COTS meeting: **COA Halifax** (Date/time TBD)

McCAIG INSTITUTE
FOR BONE AND JOINT HEALTH

PrEvention of post-traumatic contractuRes with Ketotifen 2 (PERK 2)

Taylor Stranaghan BKin & Kevin A. Hildebrand, MD, FRCSC
Cumming School of Medicine
University of Calgary

Mobility for Life.

Alberta Health Services

UNIVERSITY OF CALGARY

Outline

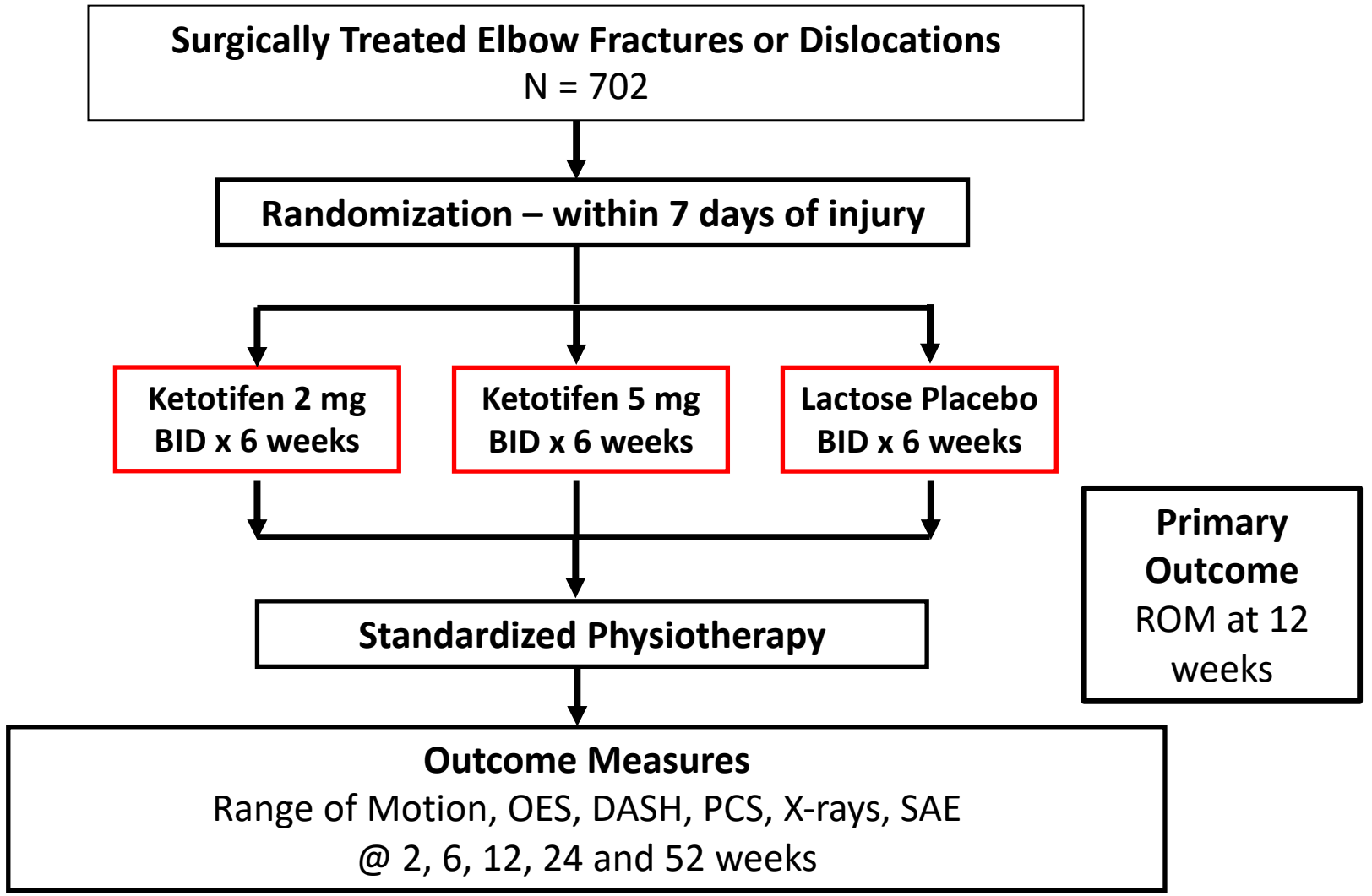
1. Study Design
2. Study Milestones
3. Approvals
4. Randomization, Drug Flow, Database
5. Questions

PERK 2

STUDY DESIGN

Multi-Centre RCT

HYPOTHESIS: Ketotifen is superior to a lactose placebo in reducing joint contracture severity in adult participants with isolated elbow fractures or dislocations

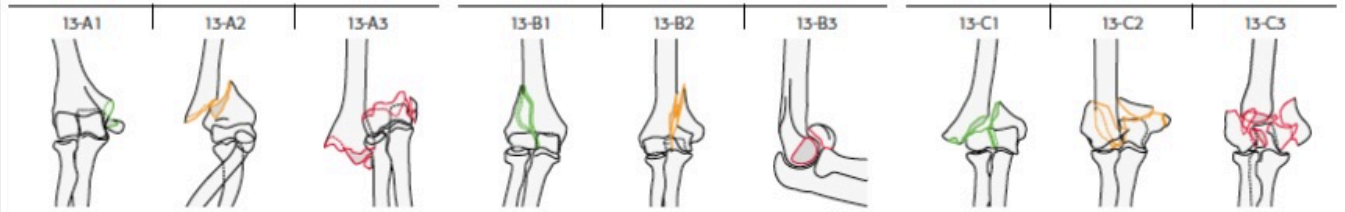


PERK 2

OTA Injury Classifications

1 Humerus

13 distal



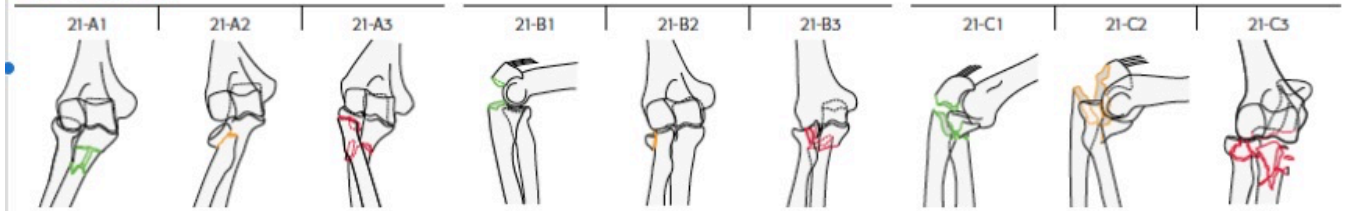
13-A extraarticular fracture
13-A1 apophyseal avulsion
13-A2 metaphyseal simple
13-A3 metaphyseal multifragmentary

13-B partial articular fracture
13-B1 sagittal lateral condyle
13-B2 sagittal medial condyle
13-B3 coronal

13-C complete articular fracture
13-C1 articular simple, metaphyseal simple
13-C2 articular simple, metaphyseal multifragmentary
13-C3 articular multifragmentary

2 Radius/ulna

21 proximal



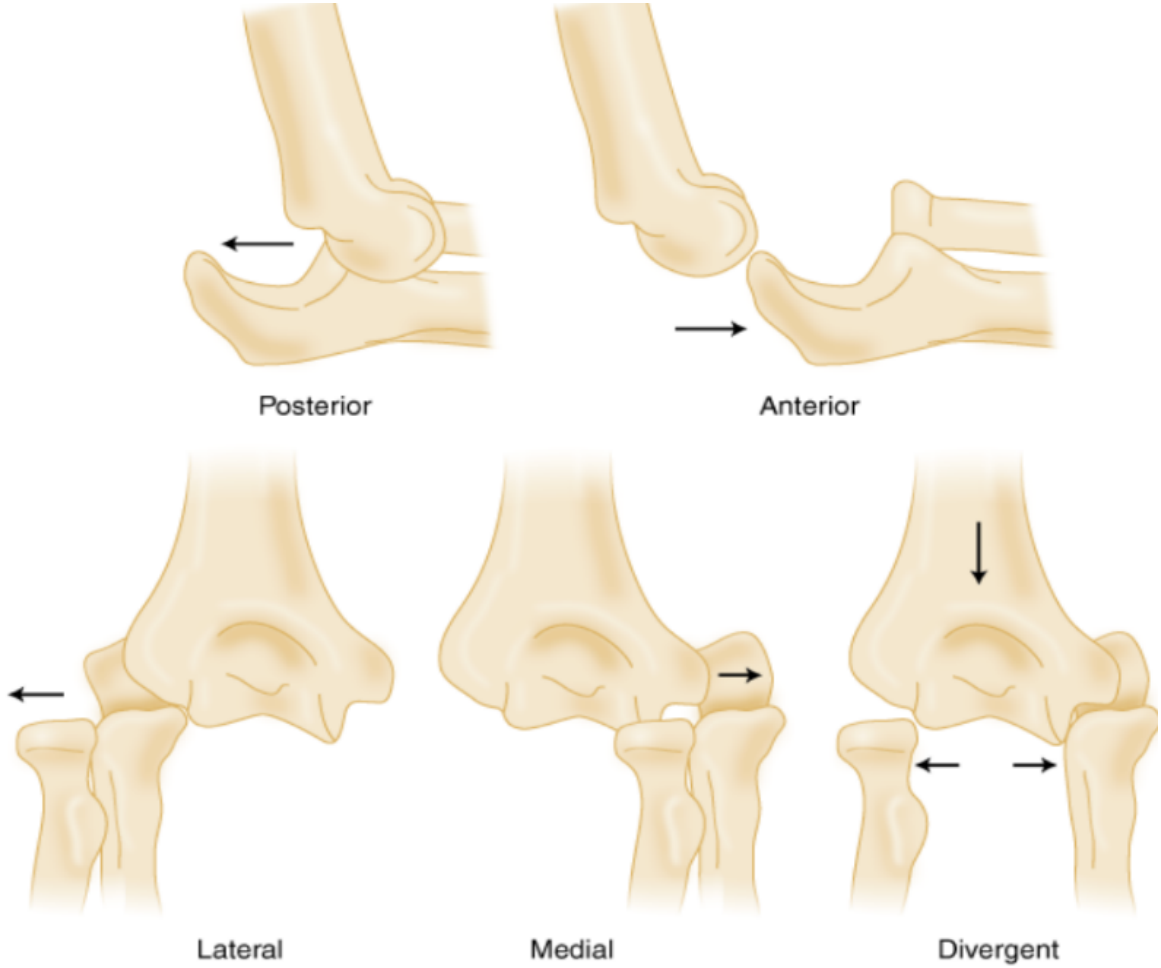
21-A extraarticular fracture
21-A1 ulna fractured, radius intact
21-A2 radius fractured, ulna intact
21-A3 both bones

21-B articular fracture
21-B1 ulna fractured, radius intact
21-B2 radius fractured, ulna intact
21-B3 one bone articular fracture, other extraarticular

21-C articular fracture of both bones
21-C1 simple
21-C2 one artic. simple, other artic. multifragmentary
21-C3 multifragmentary

PERK 2

Dislocation Classification



Trial Design: Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥ 18 years old; skeletally mature
- Injury to the elbow, with any of the following:
  - Isolated distal humerus (AO/OTA type 13)
  - proximal ulna fractures (AO/OTA type 21)
  - proximal radius fractures (AO/OTA type 21)
  - elbow dislocation
- Open fractures with or without nerve injury
- Subject presents within 7 days or less between injury and study recruitment
- Subject is scheduled for operative treatment of the elbow fracture
- Subject has negative urine pregnancy test

Exclusion Criteria

- Pre-existing elbow contracture
- Elbow arthritis (osteoarthritis, inflammatory arthritis, or nonspecific monoarticular arthritis)
- Inability to mobilize elbow within 21 days of injury or surgery
- Oral hypoglycemic medications
- History of epilepsy
- Lactose intolerance
- Unable to maintain follow-up
- Has cognitive impairment or language difficulties that would impede the valid completion of questionnaires
- Any female who is pregnant or nursing
- Severe renal impairment
- Severe hepatic impairment
- Total elbow for fracture treatment
- Prior elbow injury or surgery
- Male or female of reproductive age unwilling to use 2 methods of contraception
- Concomitant musculoskeletal or visceral injuries preventing elbow physiotherapy
- Unwilling or Unable to provide written informed consent

PERK 2

Trial Design

- Phase III
- Randomized, controlled, blinded trial
- 3 parallel groups: placebo, ketotifen 2 mg, ketotifen 5 mg
- All capsules are over encapsulated
- Administered orally, twice daily for 6 week

KETOTIFEN

- Treatment of Asthma > 40 yrs 1 – 2 mg bid
- Mast Cell Stabilizer
- Antihistamine
- Commonest side effects Maclay et al Br Medical J 1984 288:911
  - Sedation
  - Tiredness
  - Weight gain (1 – 2 kg)
  - Dry Mouth
- Wide Safety Profile
- Overdose (10 – 120 mg) – Sedation most common, no deaths
  - » Jefferys et al Br Medical J 1981 282:1755

PERK 2

STUDY MILESTONES

PERK 2

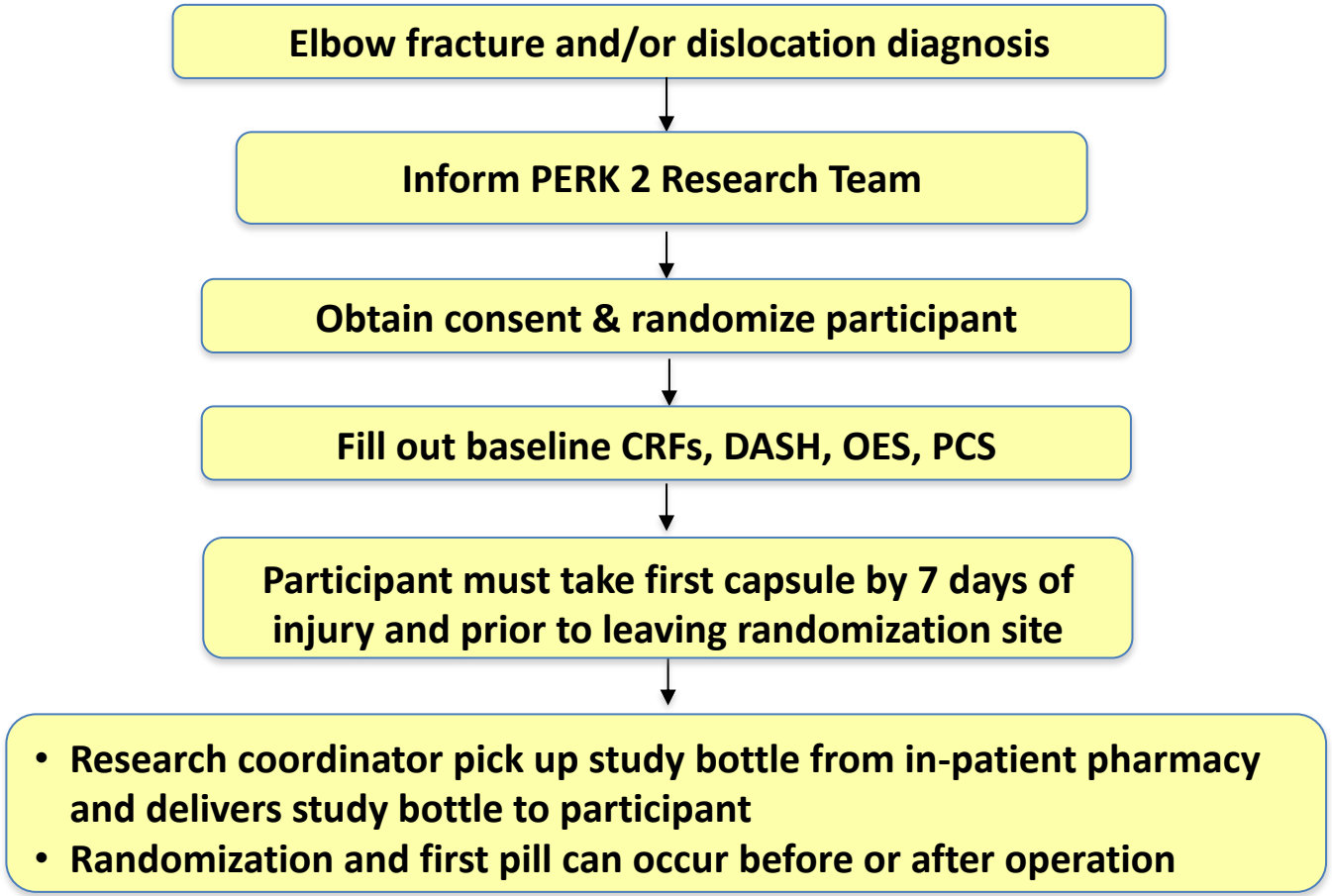
Screening / Enrolling

- Outpatient Clinic / Cast Clinic
- Inpatient Unit
  - Emergency Department
  - Day Surgery
  - Other long-term admitting unit
- Medication start after randomization
- Start can be before or after OR, within 7 days injury
  - Logistics around NPO and OR

PERK 2

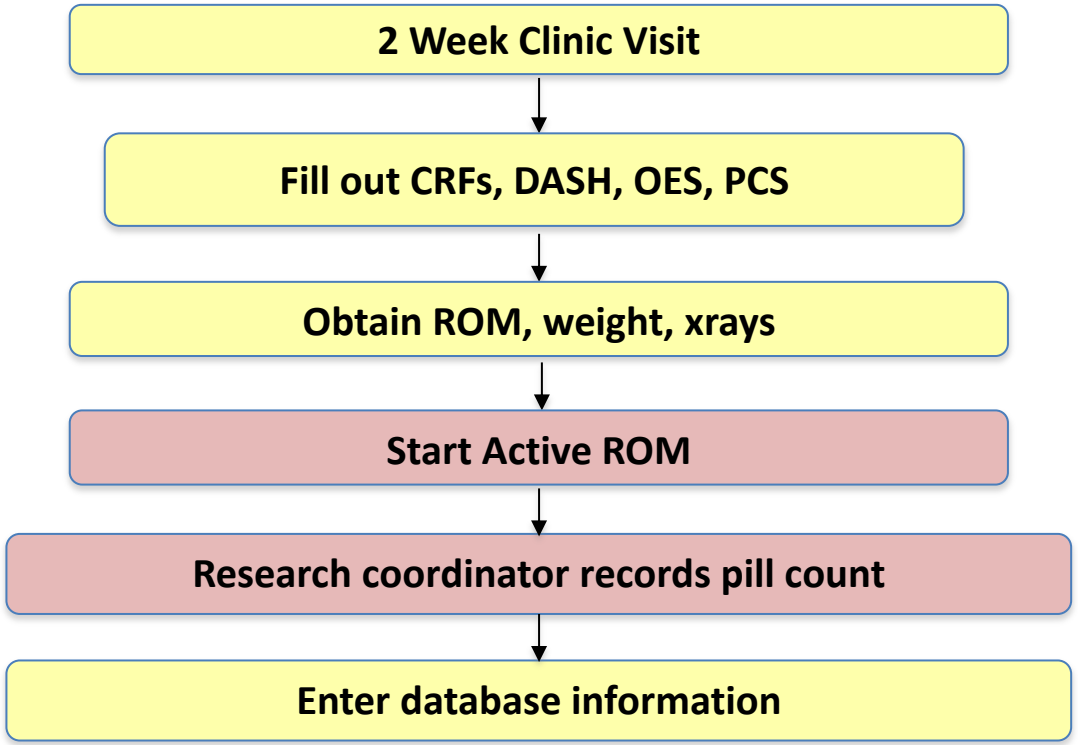
Logistics

Enrollment & Randomization



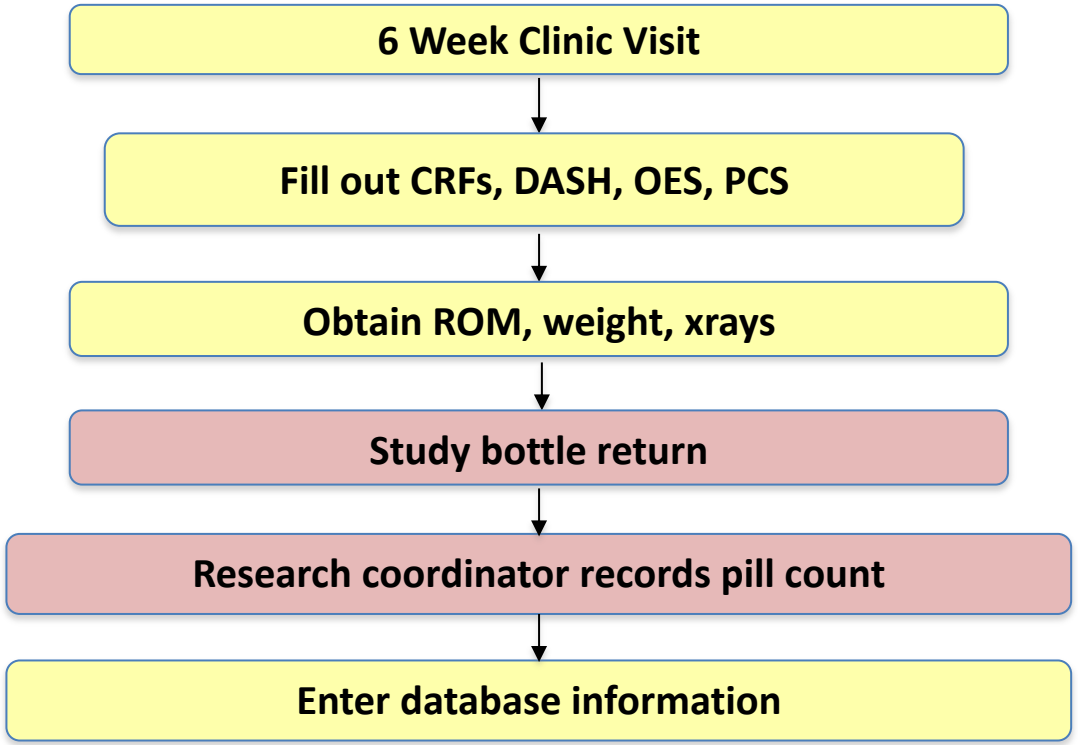
PERK 2

Sample Site Logistics Post Randomization



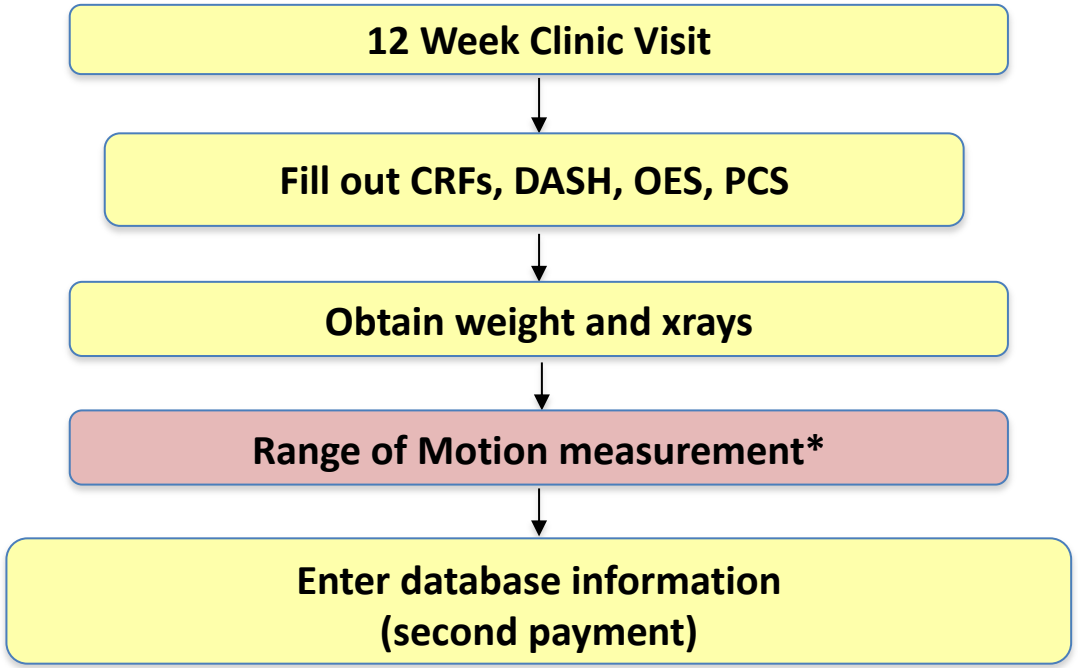
PERK 2

Sample Site Logistics Post Randomization



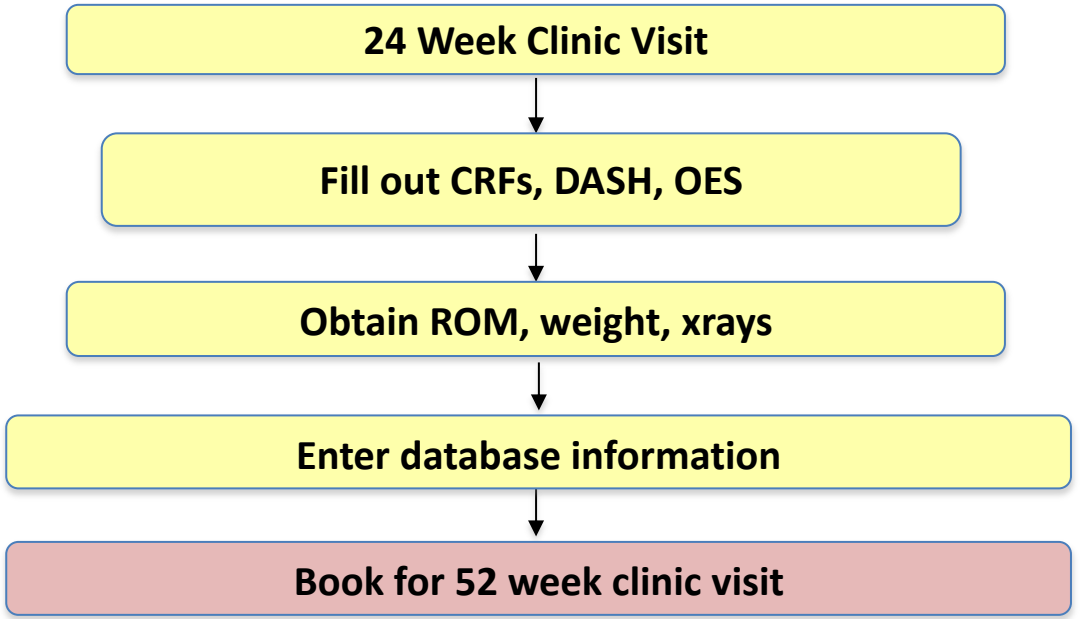
PERK 2

Sample Site Logistics Post Randomization



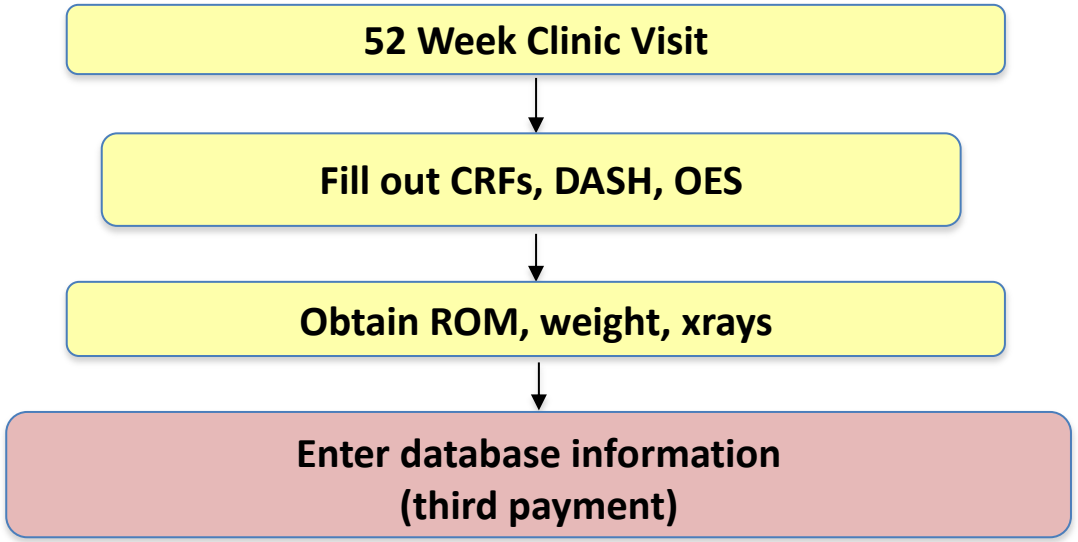
PERK 2

Sample Site Logistics Post Randomization



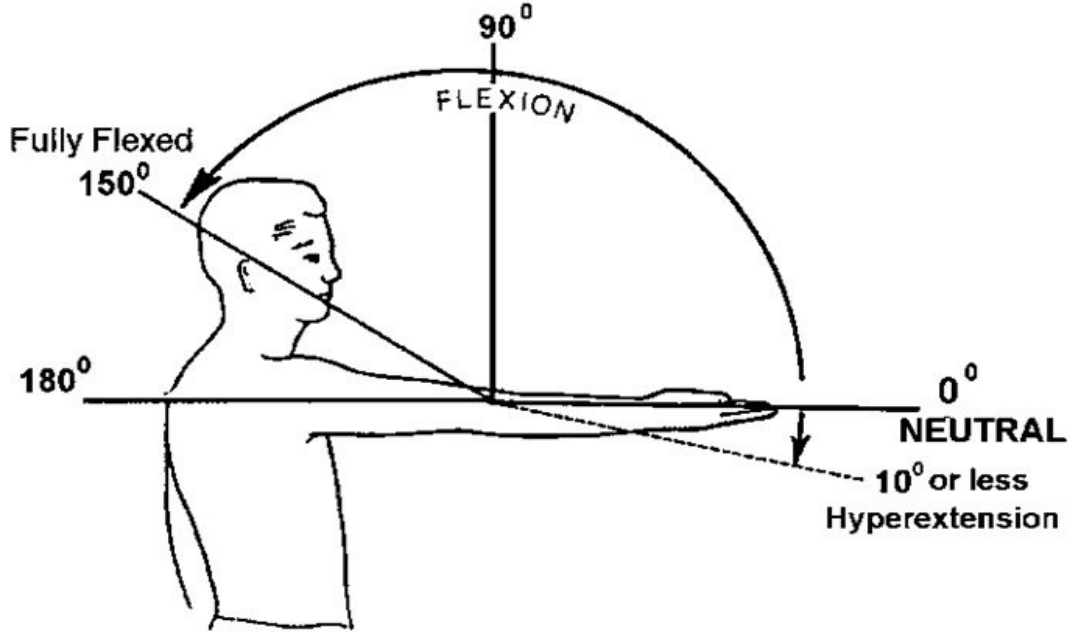
PERK 2

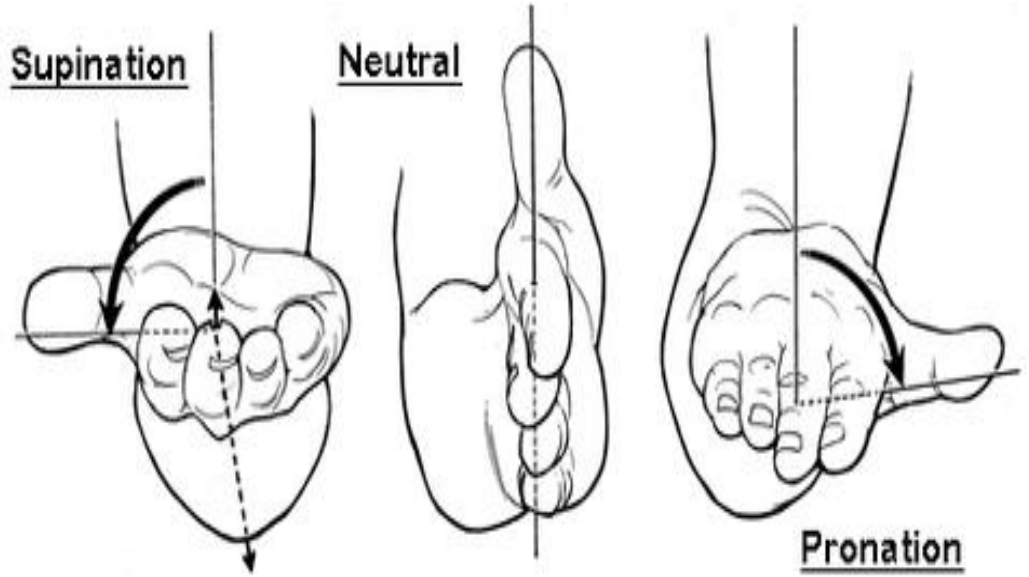
Sample Site Logistics Post Randomization



PERK 2

ROM Demonstration and Practice





PERK 2

APPROVALS

PERK 2

Trial Regulatory & Ethics

	Department of Defense HRPO		FDA IND		Health Canada		Certifications		
	Protocol Submission Form	International Research Submission Form	Form 1572	Financial Disclosure Form	Clinical Trial Site Information Form	Qualified Investigator Undertaking Form	TCPS2	GCP	Health Canada Division 5
Canadian Sites	X	X	X	X	X	X	X	X	X
American Sites	X		X	X				X	

PERK 2

RANDOMIZATION

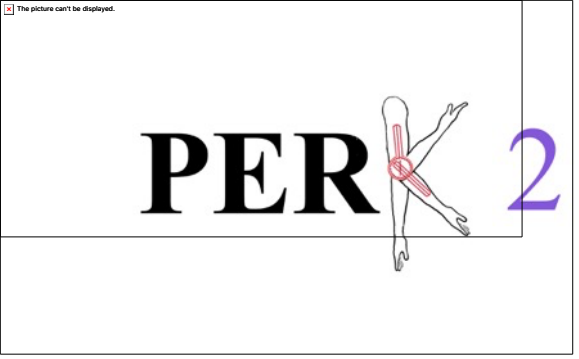
DRUG FLOW

DATABASE

PERK 2

EPICORE: Data and Drug Management Systems

- EPICORE: University of Alberta
- Electronic Data Capture (EDC):
  - REDCap
    - US FDA 21 CFR Part 11 compliant
    - GCP compliant
- Drug Tracking System
  - Randomization, Pharmacy, Bay Area Research Logistics (BARL)



REDCap Demonstration and Practice

- Screening and Randomization in REDCap
- Participant ID vs Screening ID
- Bottle number assignment
- Data entry for visits
  - Streamline substance use, medications
  - Minimize free text

PERK 2

Site Pharmacy

- Need contact information for pharmacy
- Need addresses / shipping locations
- Need to know if Medications dispensed from Pharmacy, or another spot within Hospital

PERK 2

QUESTIONS

PERK 2

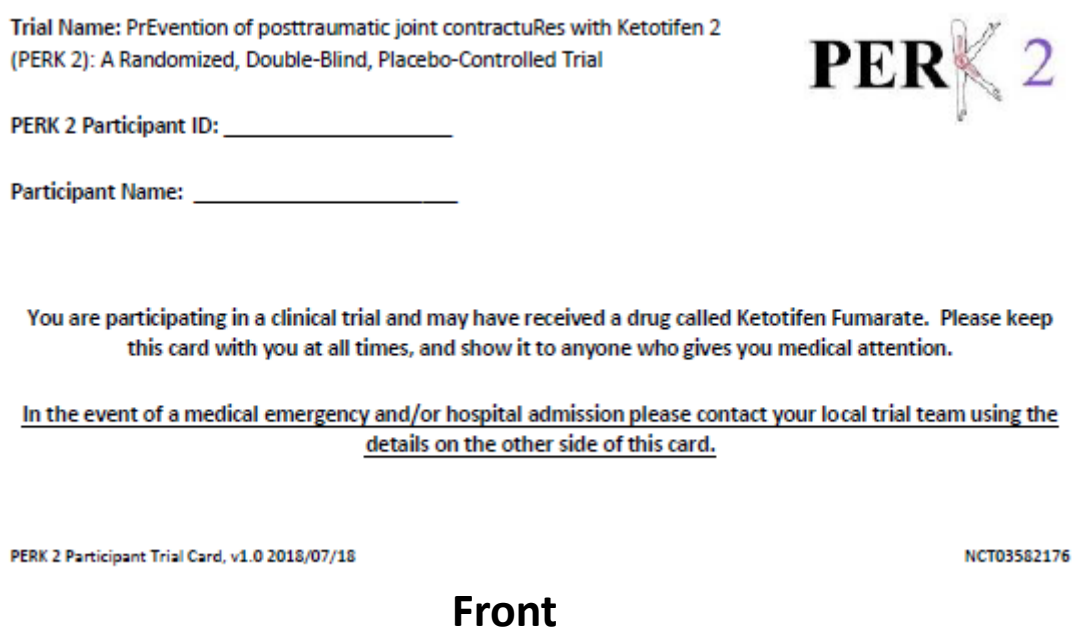
Implementation

- Site initiation visit
  - Videoconferencing? In-person?
  - Upcoming ** (SHC…)

- Enrollment start date
  - Peter Lougheed Centre: April 2019

Safety

- Participants will be provided with wallet cards (English, French or Spanish)



Trial Name: PrEvention of posttraumatic joint contractuRes with Ketotifen 2 (PERK 2): A Randomized, Double-Blind, Placebo-Controlled Trial

PERK 2 Participant ID: _____

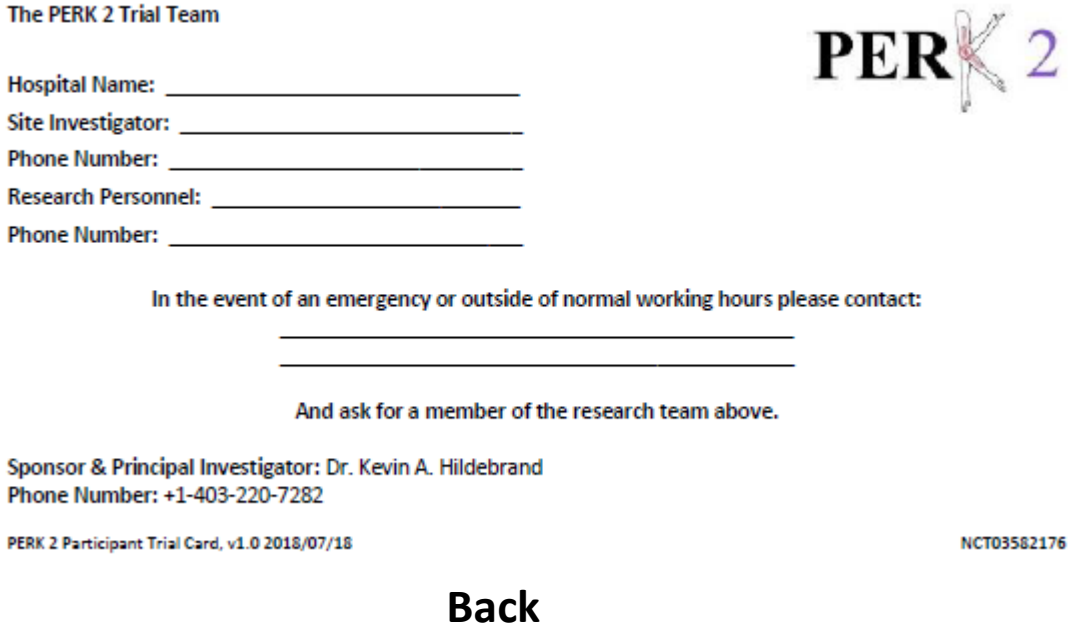
Participant Name: _____

You are participating in a clinical trial and may have received a drug called Ketotifen Fumarate. Please keep this card with you at all times, and show it to anyone who gives you medical attention.

In the event of a medical emergency and/or hospital admission please contact your local trial team using the details on the other side of this card.

PERK 2 Participant Trial Card, v1.0 2018/07/18 NCT03582176

Front



The PERK 2 Trial Team

Hospital Name: _____

Site Investigator: _____

Phone Number: _____

Research Personnel: _____

Phone Number: _____

In the event of an emergency or outside of normal working hours please contact:

_____

_____

And ask for a member of the research team above.

Sponsor & Principal Investigator: Dr. Kevin A. Hildebrand
Phone Number: +1-403-220-7282

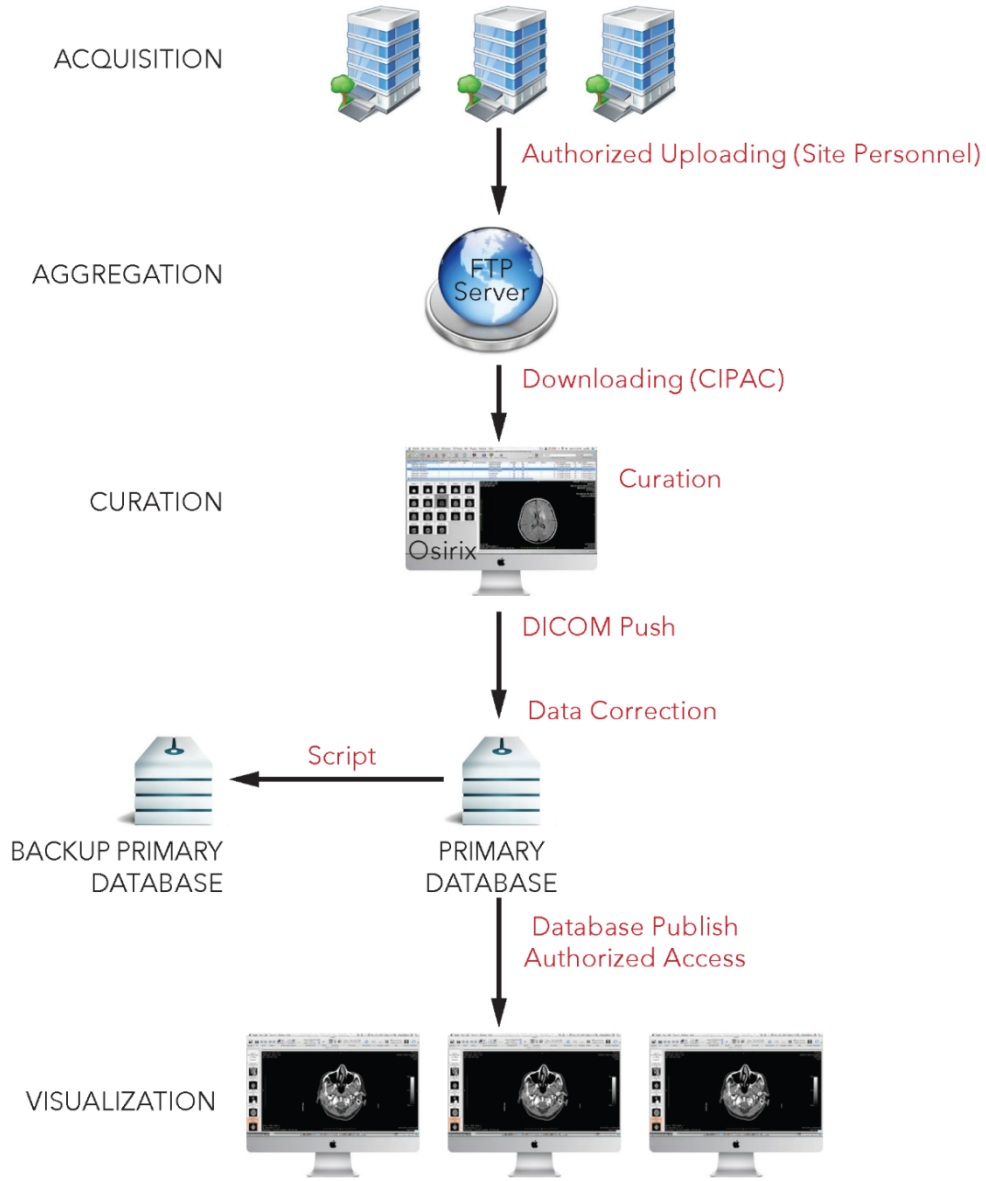
PERK 2 Participant Trial Card, v1.0 2018/07/18 NCT03582176

Back

PERK 2

Diagnostic Imaging

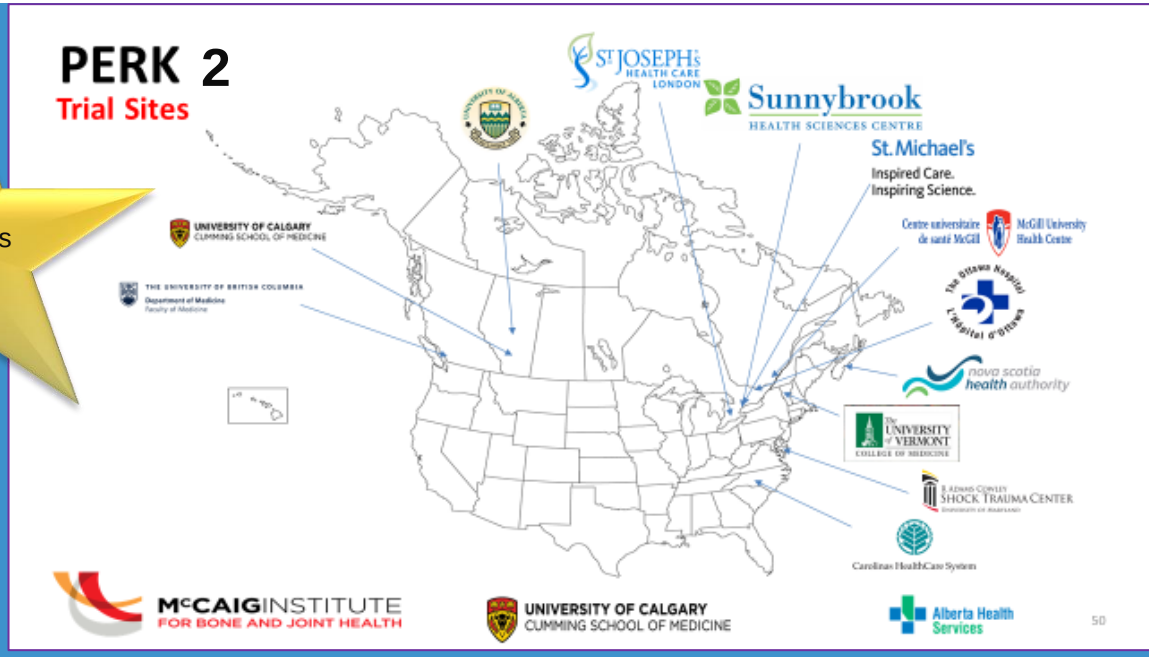
- Central storage with Calgary Image Processing and Analysis Centre (CIPAC)
- Local sites to provide images to CIPAC
- CIPAC will provide site training and ongoing trial support



PERK 2 Newsletter

Welcome to the first PERK 2 Newsletter! Thank you for attending the Investigator's Meeting at OTA this past October. We are making excellent progress with the PERK 2 trial start up!

Contracts sent out!



Milestone #1
3 sites are in the DoD review process and awaiting approval: Sturgeon, The Ottawa Hospital Civic and General

Milestone #2
PLC site approved to enroll!

Helpful Tips
1. Can submit to DoD HRPO without ethics approval

2. Check Dropbox for all trial documents

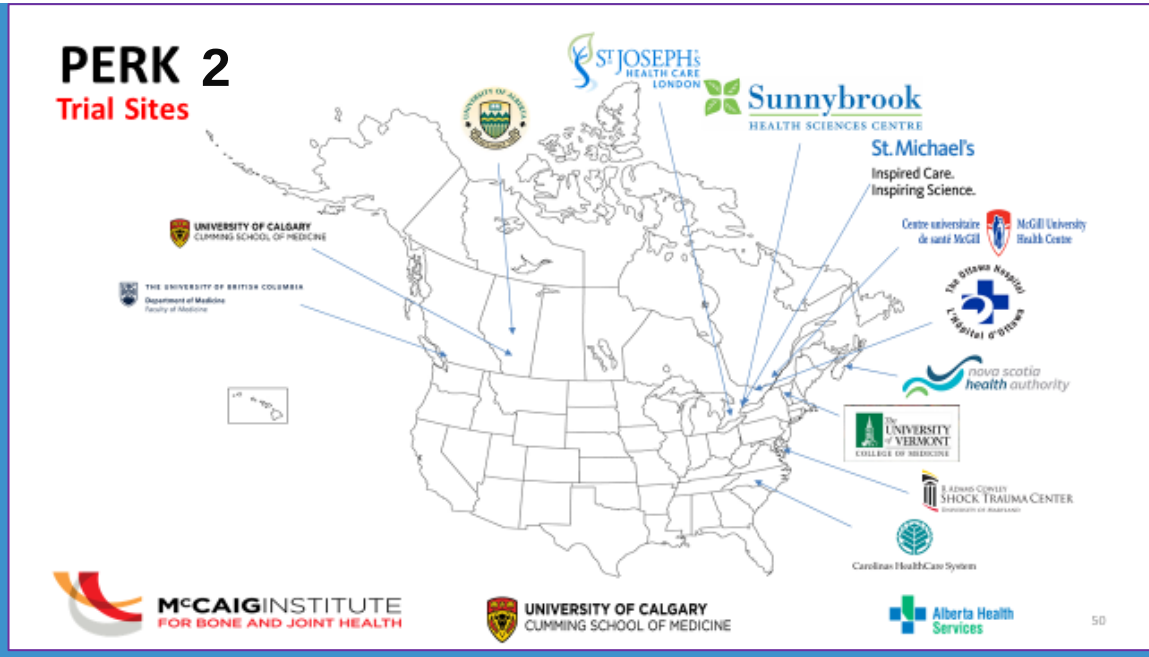
Goals
All sites submitted to DoD HRPO by March 29th

See next page for site specific regulator progress

Trial PI/Sponsor	Kevin Hildebrand	403-220-7282
Clinical Research Coordinator	Alexandra Garven	403-943-5556
Clinical Research Assistant	Taylor Stranaghan	403-943-5537

PERK 2 Newsletter

Welcome to the second installment of the PERK 2 Newsletter! We are planning an investigator's meeting at COA.



Milestone #1
7 sites are in the DoD HRPO review process and awaiting approval.

Milestone #2
The Carolinas site has all regulatory and ethics approvals.

Milestone #3
PLC site start **April 10th**!!

See next page for site specific regulatory progress

Helpful Tips
1. Submit to DoD HRPO while REB/IRB approval pending

2. Check Dropbox for all trial documents

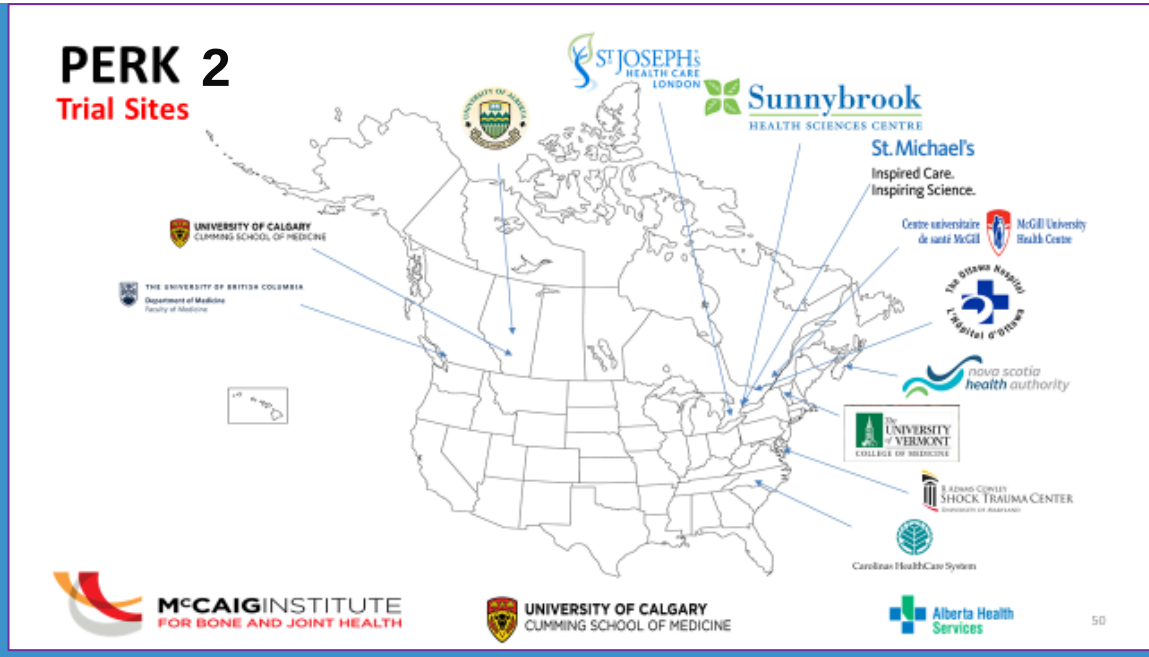
Goals
All sites submit DoD HRPO to Sponsor by **April 30th**

Trial PI/Sponsor	Kevin Hildebrand	403-220-7282
Clinical Research Coordinator	Alexandra Garven	403-943-5556
Clinical Research Assistant	Taylor Stranaghan	403-943-5537

PERK 2 Newsletter

Welcome to the third installment of the PERK 2 Newsletter!

Please join us at our Investigator's Meeting in Montreal at COA June 20th from 3:00 pm – 4:30 pm in room 514B of the Convention Centre



Milestone #1

10 sites have been submitted to DoD HRPO.

Milestone #2

2 sites have all regulatory and ethics approvals.

Milestone #3

PLC site started screening April 26th!!

See next page for site specific regulatory progress

Goal

All sites submit DoD HRPO documents to Sponsor by **May 30th**

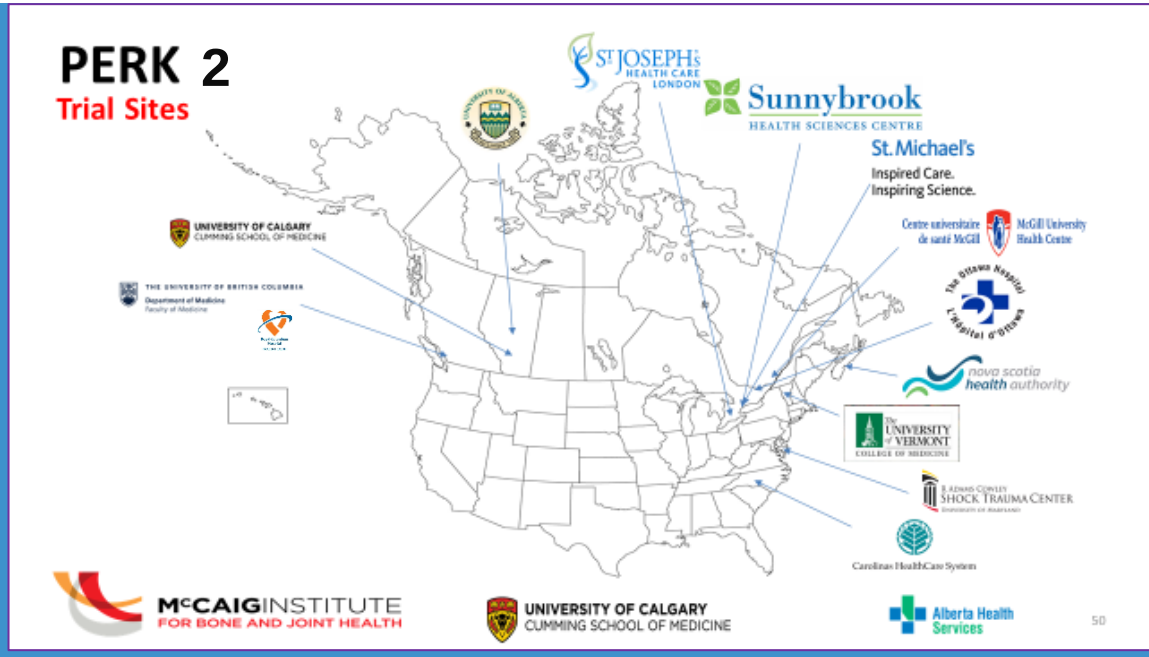
Helpful Tip

Check Dropbox for all trial documents.

Trial PI/Sponsor	Kevin Hildebrand	403-220-7282
Clinical Research Coordinator	Alexandra Garven	403-943-5556
Clinical Research Assistant	Taylor Stranaghan	403-943-5537

PERK 2 Newsletter

Please join us at our Investigator's Meeting in Montreal at COA June 20th from 3:00 pm – 4:30 pm in room 514B of the Convention Centre



Milestone #1

10 sites have been submitted to DoD HRPO.

Milestone #2

4 sites have all regulatory and ethics approvals.

Milestone #3

PLC site started screening April 26th!!

See next page for site specific regulatory progress

Goal

All sites submit DoD HRPO documents to Sponsor by **June 30th**

Helpful Tip

Check Dropbox for all trial documents.

Trial PI/Sponsor	Kevin Hildebrand	403-220-7282
Clinical Research Coordinator	Alexandra Garven	403-943-5556
Clinical Research Assistant	Taylor Stranaghan	403-943-5537

PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

July 2019 Edition, Vol. 4

PERK 2

GOALS

All sites submit DoD HRPO documents to Sponsor by **August 30th**

MILESTONES

#1: 10 sites have been submitted to DoD HRPO

#2: 4 sites have all regulatory & ethics approval

#3: 2 sites are actively enrolling!!

→ Peter Lougheed Centre (n=1)

→ South Health Centre (n=1)

TRIAL UPDATES

- PERK 2 Investigator's Meeting, Montreal 2019
  - Thank you all for joining us!
  - All questions were documented & will be put onto a FAQ document
- New Clinical Research Coordinator hired: Gerardo Duque
- Check out Dropbox for all trial documents

PERK 2 TEAM

Trial PI/Sponsor:	Kevin Hildebrand	403-220-7282
Research Coordinator:	Gerardo Duque	Starting SOON
Research Assistant:	Taylor Stranaghan	403-943-5537

PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

August 2019 Edition, Vol 5

PERK 2

GOALS

Receive DoD HRPO **approval** for 10 sites by **September 30th**

MILESTONES

#1: 10 sites have been submitted to DoD HRPO

#2: 4 sites have all regulatory & ethics approval

#3: 2 sites are actively enrolling!!

→ Peter Lougheed Centre (n=2)

→ South Health Centre (n=2)

TRIAL UPDATES

- OTA Annual Meeting in Denver, CO (September 25 – 28, 2019)
  - COTS meeting (September 26th – 7am to 12 noon)
- New Clinical Research Coordinator hired: Gerardo Duque
- Check out Dropbox for all trial documents

PERK 2 TEAM

Trial PI/Sponsor:	Kevin Hildebrand	403-220-7282
Research Coordinator:	Gerardo Duque	403-943-5556
Research Assistant:	Taylor Stranaghan	403-943-5537

PERK 2 TRIAL NEWSLETTER

Dr. Kevin A. Hildebrand

September 2019 Edition, Vol 5

PERK 2

GOALS

Receive DoD HRPO **approval** for 10 sites by **September 30th**

MILESTONES

#1: 11 sites have been submitted to DoD HRPO

#2: 4 sites have all regulatory & ethics approval

#3: 2 sites are actively enrolling!

→ Peter Lougheed Centre (n=3)

→ South Health Centre (n=4)

TRIAL UPDATES

- Site Initiation Visit for Sturgeon Community Hospital scheduled for September 10th, 2019
- We have 7 active participants enrolled in the trial!
- OTA Annual Meeting in Denver, CO (September 25 – 28, 2019)
    - o COTS meeting (September 26th – 7am to 12 noon)

PERK 2 TEAM

Trial PI/Sponsor:	Kevin Hildebrand	403-220-7282
Research Coordinator:	Gerardo Duque	403-943-5556
Research Assistant:	Taylor Stranaghan	403-943-5537

Subject: Re: Sabbatical
Date: Wednesday, July 12, 2017 at 3:11:13 PM Mountain Daylight Time
From: Andrew Carr
To: Kevin A. Hildebrand
CC: James Wright, Ann Watson
Attachments: image001.png

Dear Kevin

Thanks for making contact
Great to hear from you

We would be delighted to host you for a sabbatical

Details of the department can be found at
https://www.ndorms.ox.ac.uk
and of my group at
https://www.ndorms.ox.ac.uk/research-groups/regenerative-medicine

you will be able to find other surgical research groups on the site

we have a fair amount of trial activity including placebo controlled trials and methodological trial research
https://www.ndorms.ox.ac.uk/csm
https://www.ndorms.ox.ac.uk/research-groups/equator-network
https://www.ndorms.ox.ac.uk/research-groups/oxford-clinical-trials-research-unit
https://www.ndorms.ox.ac.uk/research-groups/surgical-interventions-trials-unit

no one is working on post traumatic elbow stiffness but we do have interests in fibrosis and inflammation which might be of value
the department is based in the hospitals and 2 institutes the Kennedy 250 scientists focussing on inflammation and immunology and the Botnar 250 scientists focussing on trials regen med and sarcoma/myeloma

your countryman Jim Wright is working with us
He would be a useful guide to the opportunities here

if you remain interested then I suggest a skype or facetime call to discuss further

all best and thanks for your interest

Andy

Prof Andy Carr ChM DSc FRCS FMedSci
Head | Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences

SABBATICAL REPORT – Kevin Hildebrand, MD, FRCSC

Time: September 1, 2018 to August 31, 2019

For my sabbatical I had 2 goals I wanted to accomplish pertinent to PERK 2. These goals were:

1) RCT Theoretical – to enhance my knowledge and skills in Randomized Clinical Trials as I am leading an investigator-sponsored randomized clinical trial.
2) RCT practical – to design and implement an investigator-initiated, US Department of Defense (DoD) funded multicentre, international randomized clinical drug trial in a surgical population, with US Food and Drug Administration (FDA) oversight.

September 1, 2018 to November 30, 2018 – Oxford University

Sponsor: Professor Andrew Carr, Nuffield Professor of Orthopaedic Surgery and Head, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS).

The purpose of my time at Oxford was to increase my knowledge and skills in Randomized Clinical Trials. The Oxford University Centre for Statics in Medicine (CSM) is located in the Botnar building of NDORMS. Within CSM is the Oxford Clinical Trials Research Unit (OCTRU) which has experience with industry- and investigator-sponsored clinical trials. It has clinicians (Physicians, Physiotherapists), epidemiologists, trialists, biostatisticians, trial managers, and research coordinators in it. A subgroup of OCTRU is the Surgical Interventions Trial Unit (SITU), where I shared an office with Alan Silman, an academic Rheumatologist. During the time of the sabbatical I was designing a US Department of Defense funded multicentre, international randomized clinical drug trial in a surgical population, with US Food and Drug Administration (FDA) oversight. A summarization of accomplishments for the 6 listed goals during the 3 months in Oxford follows.

1) RCT Theoretical

   The main activities in this goal were courses from a few hrs to 1 week in length, individual meeting with the personnel in the CSM, attending group meetings, reading relevant book chapters and journal articles. The courses I took included a 1-week Randomized Clinical Trial course at Oxford, the IDEAL course for 2 days in Bristol, UK, and 2 partial day courses at Oxford on Trial Master files and the use of Continual Reassessment Method in early phase clinical trials. The group meetings were attending a trauma conference from the Orthopaedic group at the University of Oxford John Radcliffe hospital where I learned about the James Lind Alliance and I presented on the Alberta Bone and Joint Strategic Clinical Network hip fracture pathway, sitting in on a trial management group meeting for the John Radcliffe Orthopaedic trauma group on their hip fracture cohort and imbedded hip fracture RCT's, and finally I was 1 of 5 visiting professors at the Duthie Day, the Orthopaedic trainee research day which included a presentation I gave on my upcoming RCT. I met with Professor Carr on 7 separate occasions, Professor Silman and Professor Matt

Costa 3 times, Professor Jagdeep Nanchahal 2 times, and 8 other CSM faculty one time each. There were several surgical RCTs from SITU that had been published and were the topics of some of the discussions I had with the Professors: CSAW, FIMPACT, and UKUFF on shoulder surgery including placebo surgery, Hip arthroscopy, and protocol papers and qualitative research studies embedded within the RCTs. The book chapters were related to a text associated with the 1-week RCT course.

I took many things from this goal. Randomized clinical Trials are useful when there is uncertainty, addresses causality, examines moderate treatment effect sizes, excellent at effectiveness or efficacy, and weak on assessing safety. Attrition can negate the balancing of cohorts at time of randomization. Subgroup analysis and statistical plan is best defined a priori. A protocol paper is very important to state these a priori. I learned about the EQUATOR network, with templates for many study designs / publications, including CONSORT processes for Pilot or Feasibility trials.

2) RCT practical

Several activities in the designing of the upcoming trial PrEvention of posttraumatic contractuRes with Ketotifen 2 (PERK 2) were accomplished. It is registered with ClinicalTrials.gov - Identifier NCT03582176. Two grants from the DoD support this study. The first finished while I was in Oxford and I wrote a final report and an earlier quarterly report that was overdue. The second grant had an annual report due, and I also had to submit a separate amendment request. A significant time and effort component was working with the Clinical Research Unit in the Cumming School of Medicine for an electronic data capture system using iDataFax and a randomization and drug flow platform through StudyManager. Part of this was working with MedDRA coding for adverse events and serious adverse events. I attended the Orthopaedic Trauma Association meeting in Orlando, FL Oct 17 – 19, where I met with several of the sites outside of Calgary who will be recruiting in the trial. I hired a research assistant (Taylor Stranaghan) while I was away and had weekly FaceTime sessions with her. I also worked with Medlegal to develop a master template for subsite contracts. Other activities included trial master files, trial manual, pharmacy manual, posters, scripts for screening, recruiting, and outcome measures, standard operating procedures, and the University of Calgary Audit visit prior to start up at the lead site, the Peter Lougheed Centre. The goal is to start recruiting in January 2019.

3) Writing papers

December 1, 2018 to January 16, 2019 – Calgary

I returned to Calgary where I worked from home, at shared spaces at the Peter Lougheed Centre, and at the Foothills Campus at the University of Calgary.

1) RCT Theoretical

No work in this area.

2) RCT practical

Very busy in this area. Completed: 1) CSMlegal site subcontracts with Budget attachment; 2) Interviewed 2 different monitors, confirmation of final decision pending; 3) Staff management – gave Alexandra Garven 5 weeks off (4 weeks vacation, 1 week U of C Christmas) and conducted mid-probationary review for Taylor Stranaghan, and rehired Nicole Foldessy for data entry; 4) Discussed committees with Nick Mohtadi and Tolu Sajobi, settling on a trial management group (adverse event committee to report here), trial steering committee and data safety and monitoring board committee – TOR and members pending; 5) worked on Trial manual; 6) completed FDA IND amendment sent mid December 2018 and the IND annual report sent mid January; 7) Submitted Health Canada amendment in mid December; 8) completed the quarterly DoD report for quarter ending Dec 29, 2018; 9) Reviewed PERK 2 Budget, stop payment to Maryland, outstanding payments to Carolinas and Sturgeon, not completed payments for BARL / BAHT from first DoD grant; 10) Worked on a Service agreement with CRU that had an increase of 400% on the annual maintenance fee – it is outstanding when I left and the last hurdle before starting PERK 2 at PLC; 11) Reviewed and developed a response plan for the U of C Internal audit report submitted by Linda Longpre; 12) Met with graduate student Ayo Ademola and cosupervisor Tolu Sajobi to define an area of study – methodologic issues in Orthopaedic trials – consider a) Sample size calculations using frequency and Bayesian approaches, b) Subgroup analysis, and c) missing data plus assigned him the duty of writing the protocol paper for PERK 2; 13) Held the first Trial Management Group meeting January 14 to discuss learnings from PERK 1 pertinent to PERK 2 and the Service agreement negotiations with CRU.

January 18, 2019 to February 27, 2019 – Australia and New Zealand vacation

1) RCT Theoretical

I worked with 2 potential students to do a scoping review on Drugs and contractures. I offered it first to Brock Weston although he went a different direction with the W21C. Hunter Graves took up the cause. We submitted a Singleton award application to support him. This was 8 hrs total.

2) RCT practical

For PERK 2, all of the work centered on the CRU aspect. Reviewing emails, phone calls with Alex Garven, Taylor Stranaghan, Tolu Sajobi and Rick Walker. The latest proposal Feb 22 had cut the annual maintenance fee to $31,500 / yr..

March 1, 2019 to May 31, 2019 – Calgary

1) RCT Theoretical
   No work in this area.

2) RCT practical
   Very busy in this area. Completed: 1) Shift drug flow, randomization, and database to EPICORE from CRU. The extremely expensive quote, using outdated DatFax with 2016 version and uncertainty if CRU would get 2019, interviewing EPICORE and HUB to confirm the quotes from CRU outrageous, and endorsement of EPICORE by researchers in nursing and medicine (rheumatology, interventional radiology), and pleasant, can-do, and open interactions with Yazid and Lily; 2) Monitor contract submitted to Jackie Bushekin; 3) Conducted probationary review for Taylor Stranaghan, and Annual review for Alex Garven; 4) DMC charter drafted; 5) further steps in sites coming onboard; 6) Completed quarterly report DoD; 7) Research Assistant funding competition application to University of Calgary Orthopaedics; 9) SNAPU monitoring site visit; 10) Planned a PERK 2 training session at the upcoming COA meeting in Montreal June 2019; 11) Held the second Trial Management Group meeting May 16 to discuss learnings from PERK 1 pertinent to PERK 2 and the Service agreement negotiations with CRU; 12) Submission of a job profile and job opening request to replace Alex Garven after she resigns; 13) PERK 2 started screening April 26, 2019 at the PLC; 15) completed Alberta Health Services privacy training and confidentiality.

May 1, 2019 to August 31, 2019 – Calgary

1) RCT Theoretical
   No work in this area.

2) RCT practical
   Very busy in this area. Completed: **PERK 2** 1) Randomized first participant in PERK 2 June 29; 2) Site initiation visit and reporting process developed with second site starting recruitment June 26 (South Health Campus) – first participant randomized July 2; 3) Monitor contract signed with Jackie Bushekin and refinement of a Monitoring plan document; 4) Resignation of Research Coordinator Alex Garven June 30 and hiring, onboarding and training her replacement – Gerardo Duque started July 10; 5) TSC and TMG charters drafted; 5) identifying 7 sites likely to be recruiting by October 31, 2019 having completed IRB, HRPO, HC and contract steps; 6) Completed quarterly report DoD; 7) REDCap database and Drug tracking system developed through EPIOCRE that is operational and training completed for sites recruiting; 8) Pharmacy Manual and Investigator Brochure revisions, Trial Manual, Standard Operating Procedures and Trial Master Files Development 9) PERK 2 training session at the COA meeting in Montreal June 20, 2019; 10) Held the third Trial Management Group meeting June 10 to review study performance; 11) Revised Protocol to Version 5.0 and Informed Consent Form to Version 5.0; 12) Submitted Ethics Renewal; 13) Ordered medication for new sites coming onboard, modified

Bottle labels, extended expiry date of first batch of medication sent to Calgary all through BARL; 14) Mock recruitment and reviewed screening processes; 15) Reviewed Budget current status; 16) Developed principles around site payments including separating Pharmacy from coordinator/parking/food-beverage fees and tying payments to completed data entry; 17) Developed principles around data review / queries in context of central research coordinator and monitor; 18) Development of a Statistical analysis plan for PERK 2 informed by PERK 1 analysis and findings; 19) ongoing screening, recruiting and follow up through phone and clinic visits; 20) Consideration of electronic means to collect PROMs through REDCap

(NDORMS)
Director | Botnar Research Centre
University of Oxford | Nuffield Orthopaedic Centre | Windmill Road Headington | Oxford | OX3 7LD
t: +44 (0)1865 737547 |
e: andrew.carr@ndorms.ox.ac.uk
w:http://www.ndorms.ox.ac.uk/team/andrew-carr
pa: ann watson
t: +44 (0)1865 737421
e: ann.watson@ndorms.ox.ac.uk

From: "Kevin A. Hildebrand" <hildebrk@ucalgary.ca>
Date: Wednesday, 12 July 2017 at 16:19
To: Andrew Carr <andrew.carr@ndorms.ox.ac.uk>
Cc: Ann Watson <ann.watson@ndorms.ox.ac.uk>
Subject: Sabbatical

Hi Professor Carr,

I am enquiring about the possibility of completing a 3-month sabbatical at your institution in late summer / fall of 2018. My interest in visiting your institution is to learn about your clinical trials unit, discovery and applied laboratory research, and clinical management of elbow disorders.

I am an Orthopaedic Surgeon at the University of Calgary specializing in Elbow and wrist disorders. I provide on call services at a level 2 trauma centre. I have been the Chief since 2008. We have 67 surgeons across 5 hospitals in our city of 1.2 million. My research interest is post-traumatic elbow joint contractures. My applied laboratory research has progressed to a clinical trial where we have compared a single dose of Ketotifen to placebo for the prevention of post-traumatic contractures following elbow fractures or dislocations in Calgary (ClinicalTrials.gov Identifier NCT01902017). We recruited 152 participants and the final follow up is later this month. Currently I am in the negotiation phase for a contract with the US Department of Defense (DoD) to complete a multicenter, multidose RCT comparing ketotifen to placebo. I expect to start the trial early in 2018. I continue with my laboratory research exploring other components / strategies pertinent to the myofibroblast-mast cell-neuropeptide network. I have been the colead of a Provincial implementation of a Hip fracture pathway and prevention of subsequent fragility fractures (Catch a Break).

I have attached a recent Biosketch and the abstract for the DoD grant. I visited Oxford in 2003 as an ABC fellow. The Botnar Research Centre was open at the time, and it was shortly before the major reconstruction of the clinical delivery buildings at Oxford. I am interested in spending time on my sabbatical at Oxford because the opportunities at your institution bear direct relevance on my research and clinical interests.

Thank you for considering my request. I look forward to the opportunity and developing a specific plan should it be possible.

Kevin Hildebrand, MD, FRCSC, CCPE
Division Chief, Orthopaedic Surgery
Professor, Department of Surgery
University of Calgary